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Structural Asymmetry in the Frontal and Temporal Lobes Is Associated with *PCSK6* VNTR Polymorphism

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Abstract

The nodal cascade influences the development of bodily asymmetries in humans and other vertebrates. The gene *PCSK6* has shown a regulatory function during left-right axis formation and is therefore thought to influence bodily left-right asymmetries. However, it is not clear if variation in this gene is also associated with structural asymmetries in the brain. We genotyped an intronic 33bp *PCSK6* variable number tandem repeat (VNTR) polymorphism that has been associated with handedness in a cohort of healthy adults. We acquired T1-weighted structural MRI images of 320 participants and defined cortical surface and thickness for each HCP region. The results demonstrate a significant association between *PCSK6* VNTR genotypes and gray matter asymmetry in the superior temporal sulcus, which is involved in voice perception. Heterozygous individuals who carry a short (≤ 6 repeats) and a long (≥ 9 repeats) *PCSK6* VNTR allele show stronger rightward asymmetry. Further associations were evident in the dorsolateral prefrontal cortex. Here, individuals homozygous for short alleles show a more pronounced asymmetry. This shows that *PCSK6*, a gene that has been implicated in the ontogenesis of bodily asymmetries by regulating the nodal cascade, is also relevant for structural asymmetries in the human brain.

Keywords *PCSK6* · VNTR · Laterality · Superior temporal sulcus · Language

Introduction

Hemispheric asymmetries are a fundamental organizational property of the vertebrate brain [1–4] and can be observed in brain structure and function, as well as at the level of gene expression [5]. It has been proposed that functional hemispheric asymmetries, such as handedness and language lateralization, are linked to each other [6] implicating a shared ontogenetic origin. However, the neurophysiological as well as the genetic mechanisms underlying functional lateralization are still unclear.

Using handedness as a prime example for lateralized behavior, Brandler and Parac chini [7] hypothesized that genes involved in the development of brain asymmetries and the development of brain midline structures potentially serve as the genetic foundation of functional asymmetries. In line with this hypothesis, a core biological mechanism underlying the development of asymmetries is the nodal cascade, which has been shown to influence behavioral lateralization and brain asymmetries in zebrafish [8, 9]. The asymmetric structure of the vertebrate body begins to form during embryonic development before development of brain asymmetry itself [10]. The first breaking of symmetry in the embryo results from a leftward flow of extraembryonic fluid caused by rotary ciliary movement [11]. This so-called nodal flow [12] is detected by immotile cilia of the crown cells at the edge of the node [13–16]. Due to the leftward nodal flow, nodal is more expressed on the left side of the node, which propagates to the left side of the lateral plate mesoderm. High left-side concentration of nodal leads to a self-upregulation of the *Nodal*

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gene as well as upregulation of *Lefty2* and *Pitx2* on the left side (Fig. 1) [17]. The switch of nodal from its inactive to its active state is achieved via endoproteolytic cleavage through the *PCSK6* gene product SPC4/PACE4 [18]. Therefore, *PCSK6* seems to be crucial for the development of bodily asymmetries due to its involvement in the *nodal* cascade. Concordantly, Constam and Robertson [19] examined the effects of *PCSK6* on the formation of bodily asymmetries by demonstrating impaired development of normal situs asymmetries in *PCSK6* knockout mice. Without the cleavage of nodal into its active state, threshold concentration of nodal for its positive feedback interaction with itself and forward interaction with *Lefty2*and*Pitx2* is not established resulting in impaired formation of asymmetry.

Since *PCSK6* is associated with the development of typical asymmetries within the body, it is feasible that it might also be relevant for brain asymmetries.

Therefore, several studies have investigated the influence of genetic variation within *PCSK6* on functional hemispheric asymmetries. In clinical studies, variation in the *PCSK6* gene has been associated with behavioral asymmetries like handedness in different populations. For instance, the single nucleotid

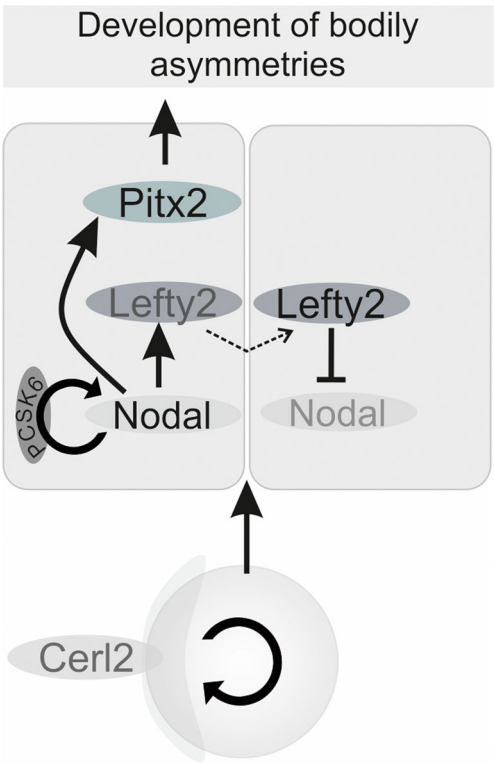

Fig. 1 The nodal cascade. In the node, clockwise rotation of cilia causes leftward flow of extracellular fluid. This leads to downregulation of *Cerl2* on the left side of the node resulting in upregulation of *Nodal*. Nodal diffuses to the lateral plate mesoderm, where it engages in a positive feedback mechanism with itself. Simultaneously, nodal activates *Lefty2* and *Pitx2*. *Lefty2* diffuses across the midline and inhibits nodal in the right lateral plate mesoderm, limiting nodal activity to the left side

polymorphism (SNP) rs9806256 located in the 14–18 intron of *PCSK6* was associated with greater right hand skill in a group of dyslexia patients [20]. Moreover, Brandler et al. [21] replicated this finding in three independent samples of people suffering from reading disorder but did not find an association between *PCSK6* polymorphisms and hand skill in a healthy control group. However, Arning et al. [22] showed an association between a variable number tandem repeat (VNTR) in *PCSK6* and direction of handedness, with heterozygous participants demonstrating lower right-handed consistency. Robinson et al. [23] partially replicated this result by showing an association between the direction of handedness in participants with higher schizotypy scores and heterozygosity in *PCSK6*. While these studies suggest an involvement of *PCSK6* in functional laterality, the effect of genes on behavior is most likely mitigated through the brain. However, to our knowledge, no study has yet examined the effect of *PCSK6* on structural hemispheric asymmetries. Therefore, we aim to investigate the relationship between the tandem repeat polymorphism in the *PCSK6* gene and the gray matter asymmetry in the human brain. Based on the findings by Arning et al. [22], we hypothesize that people who are heterozygous for long and short forms of the *PCSK6* allele show reduced gray matter asymmetries.

Methods

Participants

We tested 320 healthy adult participants (167 male and 153 female participants). All were of Caucasian descent. The participants had a mean age of 27.68 years (SD = 10.51, min = 18 years, max = 75 years) and none had a history of neurological or psychiatric diseases. Twenty-nine participants were left-handed, 291 were right-handed. Handedness was assessed using the Edinburgh Handedness Inventory [24]. Participants with a handedness laterality quotient of < 0 were categorized as left-handed and participants with a handedness LQ of > 0 were categorized as right-handed.

Genotyping

For non-invasive sampling, exfoliated cells were brushed from the oral mucosa of the participants. DNA isolation was performed with QIAamp DNA mini Kit (Qiagen GmbH, Hilden, Germany). The extracted DNA was subjected to polymerase chain reaction (PCR) using appropriate primers amplifying the 33bp (GACACAGGAAGTTGTTCTCA CCGCTGCAGCAGT) VNTR in the *PCSK6* gene at position chr15:101334170-101334495 (formerly designated as rs10523972). The PCR products were characterized by high-resolution agarose gel electrophoresis and fragment analysis

that was performed using ABI 3500xL genetic analyzer. Repeat sizing was done using Gene Mapper v3.5. Oligonucleotides were designed using Primer Express 2.0 Software (Applied Biosystems). Further details of methodology and primer sequences are available upon request.

Acquisition and Analysis of Imaging Data

All imaging data were acquired at the Bergmannsheil Hospital in Bochum (Germany) using a Philips 3T Achieva scanner with a 32-channel head coil. To estimate hemispheric anatomical asymmetries, we acquired a T1-weighted high-resolution anatomical image (MP-RAGE, TR = 8.18 ms, TE = 3.7 ms, flip angle = 8°, 220 slices, matrix size = 240 × 240, voxel size = 1 × 1 × 1 mm). The acquisition time of the anatomical image was 6 min.

Anatomical scans were segmented into gray and white matter by using surface-based methods in FreeSurfer (http://surfer.nmr.mgh.harvard.edu, version 5.3.0). Here, cortical surfaces of the T1-weighted images were reconstructed and the details of this procedure have been described elsewhere [25]. The automated reconstruction steps included skull stripping, gray and white matter segmentation, and reconstruction and inflation of the cortical surface. After preprocessing, each individual segmentation was quality controlled slice by slice and inaccuracies for the automated steps were corrected by manual editing if necessary. For the purpose of analyzing our data with regard to hemispheric asymmetries on single brain regions, we utilized the Human Connectome Project's multi-modal parcellation (HCPMMP) [26]. This parcellation scheme delineates 180 cortical brain regions per hemisphere and is based on the cortical architecture, function, connectivity, and topography from 210 healthy individuals [26]. The original data provided by the HCP were converted to annotation files matching the standard cortical surface in FreeSurfer called fsaverage. This fsaverage parcellation was transformed to each participant's individual cortical surface and generated 180 masks in each hemisphere representing single cortical brain regions yielded by the HCPMMP. In a final step, we defined for each brain region cortical thickness and surface and computed hemispheric asymmetries.

Statistical Analysis

Lateralization Quotient

For each of the 180 brain areas, we determined a lateralization quotient (LQ) following the formula:

$$LQ = [(\text{Value right hemisphere} - \text{Value left hemisphere})/(\text{Value right hemisphere} + \text{Value left hemisphere})] \times 100$$

The LQ has a range between − 100 and 100, with negative values indicating leftward asymmetries and positive values indicating rightward asymmetries. Higher values show a stronger asymmetry in the respective direction.

Additionally, we determined the absolute value of lateralization quotient (LQ) as a measure of degree of asymmetry independent of its direction. The absolute LQ has a range between 0 and 100, with higher values indicating stronger asymmetries, irrespective of direction. Further, based on the individual LQs, we determined the direction of asymmetry for each participant as a dichotomous variable by categorizing a negative LQ (leftward asymmetry) as 0 and a positive LQ (rightward asymmetry) as 1.

This resulted in three dependent variables:

1. LQ
2. Degree of asymmetry
3. Direction of asymmetry

This procedure was directly informed by the literature as Arning et al. [22] found different influences of genetic variation within *PCSK6* on LQ and degree and direction of asymmetry.

As LQ and degree of asymmetry are interval-scaled variables, we tested parametrically using univariate ANOVAs with the between-subjects factor *PCSK6* VNTR group (homozygous short, heterozygous short/long, homozygous long). As direction of asymmetry is a nominal variable, we used non-parametric Kruskal-Wallis test to compare the direction of asymmetry for the three *PCSK6* VNTR groups (homozygous short, heterozygous short/long, homozygous long). As we analyzed 180 different brain areas, Bonferroni correction resulted in a corrected significance threshold of $p = 0.05/180 = 0.00027778$.

Results

PCSK6 VNTR Results

Analyzing the intronic 33bp variable number tandem repeat polymorphism in *PCSK6* revealed 7 different alleles (3–10 copies), of which 6 and 9 copies were most frequently observed (6: allele 1, 36.3%; allele 2, 5.3% and 9: allele 1, 56.6%; allele 2, 86.9%). When dichotomizing these alleles into short (≤ 6 repeats) and long (≥ 9 repeats) alleles, 181 participants were homozygous for long alleles, 96 were heterozygous, and 17 were homozygous for short alleles. Due to

the lower number of 7 and 8 repeats, 26 participants were excluded from further analysis.

LQ for Cortical Thickness

Table 1 shows the top 10 brain areas with the lowest p values derived from the ANOVAs with the LQ for cortical thickness as dependent variable.

One out of 180 comparisons reached significance for the Bonferroni-corrected significance threshold. For area STSda (Fig. 2), the main effect of *PCSK6* VNTR group reached significance ($F_{(2, 291)} = 10.001$; $p = 0.000063$; partial $\eta^2 = 0.064$). This effect indicated more rightward lateralization (LQ = 3.29 ± 3.97) in the heterozygous long/short group than in two homozygous groups (short/short: LQ = − 0.92 ± 4.11; long/long: 1.74 ± 3.97). Bonferroni-adjusted post hoc analysis revealed a significant difference between homozygous (short/short) and heterozygous (short/long) participants (− 4.22, 95% CI [− 6.73, − 1.7], p = 0.0002) and homozygous (long/long) and heterozygous (short/long) participants (1.56, 95% CI [.35, 2.77], p = .006). There was also a significant difference between both homozygous groups (− 2.7, 95% CI [− 5.09, − .23], $p = 0.026$).

LQ for Cortical Surface

Table 2 shows the top 10 brain areas with the lowest p values derived from the ANOVAs with the LQ for cortical surface as dependent variable. None of the effects reached significance.

Degree of Asymmetry

As absolute LQ is an interval-scaled variable, we tested parametrically using univariate ANOVAs with the between-subjects factor *PCSK6* VNTR group (homozygous short, heterozygous short/long, homozygous long). As we analyzed 180 different brain areas, Bonferroni correction resulted in a corrected significance threshold of $p = 0.05/180 = 0.00027778$.

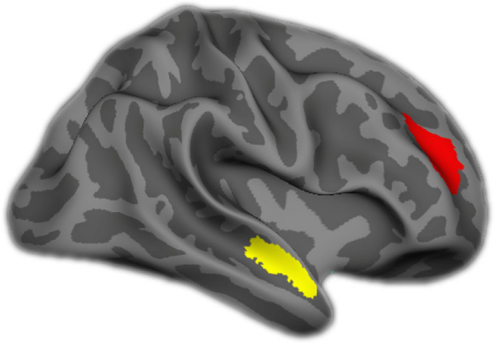

Fig. 2 Areas significantly associated with variation in PCSK6. The area STSda is shown in yellow. The area 9-46d is shown in red

Degree of Asymmetry for Cortical Thickness

Table 3 shows the top 10 brain areas with the lowest p values derived from the ANOVAs with the LQ for cortical surface as dependent variable. None of the effects reached significance.

Degree of Asymmetry for Cortical Surface

Table 4 shows the top 10 brain areas with the lowest p values derived from the ANOVAs with the LQ for cortical surface as dependent variable. Only the significant effect on area 9-46d survived Bonferroni correction. For area 9-46d (Fig. 2), the main effect of *PCSK6* VNTR group reached significance ($F_{(2, 291)} = 8.746$; $p = 0.000205$; partial $\eta^2 = 0.057$). This effect indicated stronger lateralization (LQ = 10.82 ± 1.13) in the homozygous short/short group than in the homozygous group (long/long) (LQ = 6.15 ± .35) and the heterozygous group

Table 1 Results of the ANOVAs for the cortical thickness LQs. The top 10 results with the lowest p values are shown exemplarily. * indicates significance on the Bonferroni-corrected significance threshold of $p = 0.05/180 = 0.00027778$. (*) indicates nominal significance on the $p < 0.05$ level that did not survive correction for multiple comparisons

Area	F	df	p
STSda	10.001	2	0.000063*
AVI	6.672	2	0.001 (*)
A5	5.075	2	0.007 (*)
PHT	3.779	2	0.024 (*)
a32pr	3.594	2	0.029 (*)
IFJp	3.320	2	0.038 (*)
7Pm	3.225	2	0.041 (*)
p10p	3.080	2	0.047 (*)
pOFC	3.071	2	0.048 (*)
VMV2	2.983	2	0.052

Table 2 Results of the ANOVAs for the cortical surface LQs. The top 10 results with the lowest p values are shown exemplarily. * indicates significance on the Bonferroni-corrected significance threshold of $p = 0.05/180 = 0.00027778$. (*) indicates nominal significance on the $p < 0.05$ level that did not survive correction for multiple comparisons

Area	F	df	p
d23ab	5.827	2	0.003 (*)
v23ab	5.984	2	0.003 (*)
EC	4.567	2	0.011 (*)
5mv	4.453	2	0.012 (*)
SFL	4.434	2	0.013 (*)
7Pm	4.274	2	0.015 (*)
43	3.411	2	0.034 (*)
A4	3.350	2	0.036 (*)
6d	2.600	2	0.076
RSC	2.557	2	0.079

Table 3 Results of the ANOVAs for the LQs of degree of cortical thickness. The top 10 results with the lowest p values are shown exemplarily. * indicates significance on the Bonferroni-corrected significance threshold of $p = 0.05/180 = 0.00027778$. (*) indicates nominal significance on the $p < 0.05$ level that did not survive correction for multiple comparisons

Area	F	df	p
7 m	6.439	2	0.002
6ma	4.044	2	0.019
s32	3.676	2	0.027
IFSp	2.832	2	0.061
V7	8.142	2	0.000363
A5	3.047	2	0.049
SCEF	3.137	2	0.045
24dd	2.922	2	0.055
a32pr	3.874	2	0.022
POS1	2.725	2	0.067
1	1.275	2	0.281
OP4	5.363	2	0.005
pOFC	2.356	2	0.097
11 l	2.026	2	0.134
STSda	3.054	2	0.049

(LQ = 7.3 ± .47). Bonferroni-adjusted post hoc analysis revealed a significant difference between homozygous (short/short) and heterozygous (short/long) participants (− 3.52, 95% CI [.55, 6.46], $p = 0.013$) and between both homozygous groups (4.67, 95% CI [1.84, 7.5], $p = 0.000268$).

Direction of Asymmetry

Cortical Thickness

Table 5 shows the top 10 brain areas with the lowest p values derived from the Kruskal-Wallis test.

Table 4 Results of the ANOVAs for LQs of the cortical surface. The top 10 results with the lowest p values are shown exemplarily. * indicates significance on the Bonferroni-corrected significance threshold of $p = 0.05/180 = 0.00027778$. (*) indicates nominal significance on the $p < 0.05$ level that did not survive correction for multiple comparisons

Area	F	df	p
9-46d	8.746	2	0.000205*
MT	4.997	2	0.007 (*)
d23ab	4.878	2	0.008 (*)
EC	4.436	2	0.013 (*)
SFL	4.418	2	0.013 (*)
3a	4.368	2	0.014 (*)
p10p	3.803	2	0.023 (*)
5mv	3.678	2	0.026 (*)
PFm	3.637	2	0.028 (*)
43	3.457	2	0.033 (*)

Table 5 Results of the Kruskal-Wallis test for the direction of LQs for cortical thickness. The top 10 results with the lowest p values are shown exemplarily. * indicates significance on the Bonferroni-corrected significance threshold of $p = 0.05/180 = 0.00027778$. (*) indicates nominal significance on the $p < 0.05$ level that did not survive correction for multiple comparisons

Area	χ^2	df	p
STSda	18.119	2	0.00012*
FOP4	9.547	2	0.008 (*)
TGd	8.685	2	0.013 (*)
V6A	6.843	2	0.033 (*)
TF	6.704	2	0.035 (*)
47 s	6.625	2	0.036 (*)
LIPv	6.524	2	0.038 (*)
7PL	6.304	2	0.043 (*)
p32pr	6.146	2	0.046 (*)
AVI	5.823	2	0.054

Cortical Surface

Table 6 shows the top 10 brain areas with the lowest p values derived from the Kruskal-Wallis test with the direction of LQs for cortical surface as dependent variable. None of the effects survived Bonferroni correction.

Discussion

Results from different studies provide evidence for an association of *PCSK6* variation and distinctive aspects of human handedness, thus supporting its likely role as a candidate for involvement in the biological mechanisms that underlie the establishment of typical brain lateralization. The aim of the present study was to investigate the influence of the VNTR polymorphism in *PCSK6* on the gray matter asymmetry in the human brain.

We investigated two different dependent variables, cortical surface, and cortical thickness, and calculated three different

Table 6 Results of the Kruskal-Wallis test with the direction of LQs for cortical surface. The top 10 results with the lowest p values are shown exemplarily. * indicates significance on the Bonferroni-corrected significance threshold of $p = 0.05/180 = 0.00027778$

Area	χ^2	df	p
d23ab	10.344	2	0.006 (*)
PHT	8.736	2	0.013 (*)
PSL	8.050	2	0.018 (*)
STV	6.900	2	0.032
RI	6.822	2	0.033
a24pr	6.611	2	0.037
A4	5.803	2	0.055
VMV2	5.690	2	0.058
6a	5.271	2	0.072
PGs	5.142	2	0.076

indices from these variables: LQ, degree, and direction of asymmetry, based on a previous study [22].

We found an association between the 33bp VNTR in the *PCSK6* gene and gray matter asymmetry in area dorsal anterior superior temporal sulcus (STSda), which is involved in language processing and lies adjacent to the planum temporale (PT). Here, individuals who were heterozygous for a short (≤ 6 repeats) and a long (≥ 9 repeats) allele showed stronger rightward asymmetry. Further, we found an association between variation in *PCSK6* and the degree of lateralization in the middle frontal gyrus (Area 9-46d). To our knowledge, this is the first study to show an association between *PCSK6* and structural brain asymmetries. Thus far, previous research has only shown an association between *PCSK6* and asymmetries on a behavioral level.

The STS in both hemispheres is involved in the processing of language. In the right hemisphere, the STS as part of the temporal cortex partakes in the processing of non-linguistic properties of language like prosody, which consists of rhythm and intonation of speech. The latter was found to be related to right hemispheric activation in the anterior STS [27]. Moreover, aspects of voice processing are related to activity in the right STS [28, 29]. The anterior part of the STS seems to be specialized in recognition of voice characteristics, as performance in voice recognition tasks correlates with activity in this area [30]. Similar to other language-related areas (e.g., [31]), the STS shows a macrostructural asymmetry. The sulcus is deeper in the right hemisphere [32], which seems to be a feature exclusive to the human brain [33]. The left STS on the other hand is involved in encoding of semantic meaning [34] and resolving speech intelligibility [35]. Moreover, there is neurophysiological evidence that the left temporal cortex is specialized in processing of fast temporal changes in auditory signals that are underlying stop consonants which are relevant for comprehension of linguistic information [36]. Here, the focus of research has been especially on the planum temporale (PT), which is probably the most asymmetric structure in the human brain with approximately 78% of humans displaying a bigger surface area on the left [37]. Further, its microstructural organization [38–43] indicates a predisposition for processing of temporally sensitive material like speech [44–46]. This microstructural architecture has been linked to processing speed in vivo [47]. These studies link the structural makeup of the PT to its functional specialization. A similar link may be true for the superior temporal sulcus. As the STS shows a functional asymmetry in voice recognition, it could be possible that its structural asymmetry may support this specialization. While most language-related functions show a leftward lateralization [48], both hemispheres contribute to language comprehension [49]. Language comprehension has been proposed to be a complex process, whose components show different patterns of lateralization [50], with the higher order comprehension depending on temporal sensitive processes becoming more left lateralized while the right hemisphere partakes more in the perception of pitch patterns and spectral processing, like music [36]. The association between *PCSK6* and functional lateralization has frequently been found in cohorts with dyslexia. Individuals with dyslexia display difficulties in the acquisition of age-appropriate reading abilities [51]. As reading relies on language-related areas and individuals with dyslexia display altered asymmetry in these areas [52], this suggests a link between structural and functional asymmetries and variation in *PCSK6*. Asymmetry in language functions has been related to other functional asymmetries, especially handedness: right handers show stronger leftward asymmetry for language-related function while left handers more frequently display atypical language lateralization despite unchanged macroscopic asymmetries [53]. The prevalence of atypical language lateralization rises with stronger left handedness, with mixed handers having a lower prevalence of moderate right lateralization than moderate right and left handers and mixed and strong left handers [54, 55].

Different researchers have proposed genetic theories about the origin of hand preference (e.g., [56, 57]). Despite previous research indicating a genetic component [58, 59], there has been limited success in finding genetic correlates of handedness (for review, see [60]).

Like the genetic basis of handedness, the genetic basis for language lateralization still needs further investigation. It has been speculated that there is partial pleiotropy between handedness and language lateralization, especially with an overlap between genes influencing axis formation and neurotransmitter systems [61]. A recent study by Schmitz et al. [62] found a small overlap between gene ontology groups related to handedness and language lateralization, further supporting the idea of partial pleiotropy. Since handedness has previously been related to *PCSK6*, the current results point to an overlap in the developmental mechanisms for both asymmetries.

However, the relationship between structural and functional asymmetries is not unambiguous. For example, no structural correlates of handedness have been found in cortical surface area [63], in cerebral cortex volume [64], nor studies using voxel-based morphometry [47, 65]. Moreover, studies investigating situs inversus, a condition characterized by inverted body asymmetries, could show unchanged functional asymmetries during altered structural asymmetries [66–68]. This prompts the question whether structural and functional asymmetries rely on separate developmental mechanisms with partial pleiotropy as suggested for handedness and language, and which genes may play a role in this interaction. A candidate gene for the link between *PCSK6* and language-related areas may be procured via the influence of *FOXP2*. The transcription factor *FOXP2* influences the formation and function of striatal medium spiny neurons involved in integration of dopaminergic signals relevant during language development [69]. *FOXP2* also directly targets *PCSK6* [70] and may thus influence the development of structural asymmetries.

However, it is important to consider that effects of variations in *PCSK6* were not confined to a region in the superior temporal cortex, but were also evident in the frontal cortex, i.e., in region 9-46d. As shown in Fig. 2, the asymmetry found for 9-46d encompasses the middle frontal gyrus and partly the inferior frontal gyrus. Even though structural-functional relationships in the frontal cortex are intricate, especially cognitive control processes or executive functions are mediated by the frontal cortex [71]. However, cognitive control is an umbrella term encompassing different sets of cognitive operations [71]. Interestingly, overarching conceptual considerations suggest that different sets of cognitive operations involved in cognitive control show associations with prefrontal cortex structure along a rostro-caudal axis [72, 73]. In particular, it has been suggested that anterior and posterior regions in the lateral prefrontal cortex mediate episodic and contextual control, respectively [72, 73]. Contextual control relates to the processing of signals/information that guide behavior in the immediate context/situation; episodic control refers to past events/context of a certain kind allowing that past events can define a new set of rules for action selection in an immediate situation [73]. Interestingly, it has been suggested that especially BA46 is associated with episodic control [73–75], i.e., determines performance in situations where different actions need to be put in a chain to subserve goal-directed behavior. Interestingly, it has been shown that BA46 and adjacent regions play a central role in the "multiple demand system" [76], which is involved in diverse cognitive demands, and associated with standard tests of fluid intelligence [76, 77]. This system is particularly important when goals are achieved by assembling and interrupting a series of subtasks [74, 78]. From that perspective, it is possible that variations in *PCSK6* should also affect specific subprocesses during cognitive control and hence functions going significantly beyond the currently considered relevance of *PCSK6* gene variations in handedness and language-related processes.

Conclusion

The current study found an association between a 33bp *PCSK6* VNTR and gray matter asymmetry in the superior temporal sulcus. *PCSK6* is a relevant gene for left-right axis formation, which later affects asymmetric brain formation and functioning. Our findings show for the first time that *PCSK6* is not only relevant for handedness as suggested by previous studies, but also for structural brain asymmetries.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

Abbreviations *SNP,* single nucleotid polymorphism; *VNTR,* variable number tandem repeat; *PCR,* polymerase chain reaction; *HCPMMP,* human connectome project's multi-modal parcellation; *LQ,* lateralization quotient; *STSda,* superior temporal sulcus dorsal anterior; *9-46d,* central portion of the dorsolateral prefrontal cortex; *PT,* planum temporale

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