# Chapter 10

# Human Brain Volume: What's in the Genes?

Jiska S. Peper, Marcel P. Zwiers, Dorret I. Boomsma, René S. Kahn, and Hilleke E. Hulshoff Pol

## Introduction

The human brain continues to grow considerably after birth. Compared to measurements taken at birth (mean, SD was 34.9, 1.1 cm), head circumference was found to increase by more than 30% in the first year (46.6, 1.3 cm); between 1 and 4 years of age it increased by another 9% (50.9, 1.4 cm) and between 4 and 8 years by an additional 4% (53.4, 1.4 cm) in a normal cohort (Gale, O'Callaghan, Bredow, & Martyn, 2006). Magnetic resonance imaging (MRI) research has shown that at 6 years of age total cerebral volume has reached 95% of its adult volume (Giedd et al., 1999). However, the brain continues to show dynamic changes from childhood into adulthood in overall gray and white matter and in subcortical structures. In early adolescence gray matter starts to decrease (Giedd et al., 1999), whereas overall white matter volume still increases (Bartzokis et al., 2001; Giedd et al., 1999; Paus et al., 1999). Also, subcortical structures show developmental changes after childhood. For instance, the thalamus and caudate nucleus decrease with age (Sowell, Trauner, Gamst, & Jernigan, 2002) and the posterior hippocampus increases with age, whereas the anterior hippocampus decreases with age (Gogtay et al., 2006) (for a review on brain maturation, see Toga, Thompson, & Sowell, 2006).

The contribution of specific genes and environmental factors to these developmental brain changes is currently not understood. However, it is known that in adulthood, the extent of variation in human brain volume is highly heritable, with estimates between 80 and 90% (Baaré et al., 2001; Pennington et al., 2000; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000). Most heritability estimates of brain volumes are based on data from monozygotic twin pairs (MZ, who are nearly always genetically identical) and dizygotic twin pairs (DZ, who share on average 50% of their segregating genes). If brain volumes of monozygotic twin pairs resemble each other more closely than those of dizygotic twin pairs, it can be inferred that variation of brain volumes is under genetic control. These findings from twins can be generalized to the general (singleton) population, particularly after correcting for head size or intracranial volume (Hulshoff Pol et al., 2002).

Importantly, the high heritability of brain volume is functionally relevant. For instance, the association between brain volumes and intelligence was found to be of genetic origin (Posthuma et al., 2002) and the association between frontal gray matter volume and intelligence is suggested to be due to genetic factors (Thompson et al., 2001; Toga & Thompson, 2004). Recently, the association of intelligence with frontal, occipital, and parahippocampal gray matter and connecting white matter was found to be influenced by genes common to brain structure and intelligence (Hulshoff Pol et al., 2006). These findings demonstrate that a common set of genes may underly the association between brain structure and cognitive functions. However, in elderly twins, the associations between fronto-temporal brain volumes and executive function were found to be due to common environmental influences shared by twins from the same family (Carmelli, Reed, & DeCarli, 2002). These results point to the possibility that overlapping sets of genes or common environmental influences cause variation in two distinct phenotypes. However, other, causal, models are also consistent with the findings. It might be, for example, that a higher level of cognitive function leads a person to select an environment that also increases brain size. The genetic influence on brain size then simply reflects the genetic influences on cognition. Thus, the specific mechanism, pathways, and genes that are involved in human brain morphology and its association with cognitive functions remain elusive.

A few studies have been published in which particular genetic polymorphisms (a gene with at least two relatively common variants, also called alleles) are associated with variation in brain structure. However, without some prior assumptions about which genes are good candidates,

J.S. Peper (✉)
Department of Psychiatry, University Medical Center, Utrecht, The Netherlands
e-mail: j.s.peper@umcutrecht.nl

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this may be comparable with searching for a needle in a haystack. Another approach to search for genes involved in human brain volume might be to study subjects with a known genetic makeup or a known genetic abnormality, i.e., groups in which the genetic variant is known, and to search for abnormalities in their brain volumes. This approach has also been applied to study genes involved in cognitive impairments in subjects with mental retardation (Nokelainen & Flint, 2002).

Here we review the studies on the influence of genes onto human brain volumes using quantitative magnetic resonance imaging (MRI). To this end, twin studies are reviewed to assess the heritability of human brain volume variation in the general population. In addition, brain structures in patients with diseases caused by mutations in genes located on autosomal chromosomes are discussed. For this purpose, MRI brain studies on diseases with a clear genetic etiology were included, i.e., Huntington's disease (expansion of triplet repeat on chromosome 4), Down syndrome (21-trisomy), Williams syndrome (hemideletion on chromosome 7q11.23), and Velocardiofacial syndrome (deletion on chromosome 22q11). Finally, other genetic approaches to the search of genes in brain structure are discussed. These other approaches include studies on brain volume of families with a particular genetic makeup, studies searching for genes in subjects with brain morphological abnormalities, and studies on the association of brain volumes with genetic polymorphisms in candidate genes in healthy subjects.

## Current Research

### *Methods*

A PubMed indexed search was carried out for each of the three different approaches, with a limitation for human subjects and the following keywords: (1) (brain volume) or (white/gray matter) and ((twin) or (heritability)); (2) (brain volume) or (white/gray matter) and ((Huntington's Disease) or (Down syndrome) or (Williams Syndrome) or (Velocardiofacial Syndrome)); and (3) (Brain volume/abnormality) or (white/gray matter) and ((polymorphism) or (genes)). All the abstracts were inspected ($n$=260), and papers written in English, using structural magnetic resonance imaging (MRI) were selected. These included volumetric MRI (both global and focal measures), voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) (for information on white matter integrity). Case studies or qualitative studies were not included. These selection criteria resulted in 90 papers coming from the following topics: twin studies ($n$=18), Huntington's disease ($N$=20), Down syndrome ($N$=13), Williams syndrome ($n$=14), Velocardiofacial syndrome ($N$=14), and other genetic approaches ($N$=11).

If available, information on the number of subjects, $p$-values/effect sizes, age of the sample, and heritability estimates was extracted from the papers.

### *Results*

#### Twin Studies and Human Brain Morphology

To determine the relative contribution of genetic, common, and unique environmental influences on variation in brain structures, the (extended) twin model is a powerful approach (Posthuma & Boomsma, 2000). For genetic influences (heritability), the extent to which brain structures of monozygotic (MZ) twin pairs resemble each other more than in the case for dizygotic (DZ) twin pairs is the determining factor. However, in addition to genetic influences, common (or shared) environmental influences may play a role in explaining resemblances. The presence of shared environmental factors is suggested when correlations in DZ twins are larger than half the MZ correlation (Boomsma, Busjahn, & Peltonen, 2002). A first impression of the importance of unique environmental factors is obtained from the extent to which MZ twins do not resemble each other.

Brain structure in healthy MZ and DZ twin pairs was first quantitatively studied using computed tomography (CT) (Reveley, Reveley, Chitkara, & Clifford, 1984) (Table 10.1). In this study it was found that lateral ventricle variation was mostly explained by genetic factors. Later studies using MRI found high heritability estimates of global brain measures including intracranial volume (>81%) (Baaré et al., 2001; Carmelli et al., 1998; Pfefferbaum et al., 2000) and total brain volume (66–97%) (Baaré et al., 2001; Bartley, Jones, & Weinberger, 1997; Pennington et al., 2000; Wright, Sham, Murray, Weinberger, & Bullmore, 2002). The first twin-sibling study to measure the genetic contributions to variation in global gray and white matter found heritability estimates of 82% for gray matter and 88% for white matter (Baaré et al., 2001). The volumes of each cerebral hemisphere showed 65% heritability (Geschwind, Miller, DeCarli, & Carmelli, 2002). For variation in cerebellar volume a heritability of 88% was reported (Posthuma et al., 2000).

A number of global brain areas seem to be mainly under environmental control. For example, this was found for the overall gyral patterning of the cortex (Bartley et al., 1997; Eckert et al., 2002). Common and unique environmental factors explained the individual variation in lateral ventricle volumes (Baaré et al., 2001; Wright et al., 2002). However, individual differences in lateral ventricle size were mainly of genetic origin in a study consisting of elderly

**Table 10.1** Twin studies on brain volume

| Brain area | Authors | Group size | Age (years) | Heritability |
|---|---|---|---|---|
| Lateral ventricles | Reveley et al. (1984)* | 18 MZ, 18 DZ | *NA* | 82–85% |
| Total brain, gyral patterns | Bartley et al. (1997) | 10 MZ (6 males), 9 DZ (3 males) | MZ: 31 (19–54)<br>DZ: 23 (18–29) | TB: 94% Gyral patterns: 7–17% |
| Intracranial volume (IC) and white matter hyperintensities (WMH) | Carmelli et al. (1998) | 74 MZ, 71 DZ (males) | 68–79 years | IC: 91%<br>WMH: 71% |
| Total cerebral volume | Pennington et al. (2000) | RD: 25 MZ (12 males), 23 DZ (16 males)<br>Non-RD: 9 MZ (4 males), 9 DZ (4 males) | RD: MZ 17.1, DZ 16.8<br>Non-RD: MZ 19.4, DZ 18.7 | 97% (two factors: neocortex 56%, subcortex 70%) |
| Intracranial volume (IC), midsagittal corpus callosum (CC) and mids lat ventricles (LV) size | Pfefferbaum et al. (2000) | 45 MZ, 40 DZ (males) | MZ 72.2<br>DZ 71.4<br>68–78 | IC: 81 %<br>CC: 79%$<br>LV: 79% |
| Intracranial volume, total brain, gray and white matter, lateral ventricles | Baaré et al. (2001) | 54 MZ (33 males)<br>58 DZ (17 males, 21 OS)<br>34 sibs | MZM: 31.2, MZF: 34.1,<br>DZM: 30.3, DZF:<br>30.6, OS: 30.3, sibs: 29 | IC: 88%<br>TB: 90%<br>GM: 82%<br>WM: 87%<br>LV: C: 59%, E 41% |
| Microstructure corpus callosum (with DTI) | Pfefferbaum et al. (2001) | 15 MZ, 18 DZ | *NA* | Relative proportion G:E in CC size: 5:1, microstructure: 3:1 |
| Hippocampus | Sullivan et al. (2001) | 45 MZ, 40 DZ (males) | MZ 72.2<br>DZ 71.4<br>68–78 | 40% |
| Frontal lobes, Broca and Wernicke's areas | Thompson et al. (2001) | 10 MZ (5 males), 10 DZ (5 males) | 48.2 (±3.4) | Frontal lobe 90–95% |
| Planum temporale asymmetry | Eckert et al. (2002) | 27 MZ, 12 DZ (all males) | MZ: 6.9–16.4<br>DZ: 6.1–15.0 | *NA* |
| Cerebral hemispheres Cerebral asymmetry/handedness | Geschwind et al. (2002) | 72 MZ, 67 DZ (males) | MZ: 72.3<br>DZ: 71.8 | Both hemispheres: 65% In left handers: less genetic control of hemispheres. More $c^2$ influence on left hemisphere |
| Cerebellum | Posthuma et al. (2000) | 54 MZ (33 males)<br>58 DZ (17 males, 21 OS)<br>34 sibs | MZM: 31.2,<br>MZF: 34.1,DZM: 30.3,<br>DZF: 30.6, OS: 30.3,<br>sibs: 29 | 88% |
| Total brain, lateral ventricles (LV) and regional GM (with factor analysis) | Wright et al. (2002) | 10 MZ (6 males), 10 DZ (4 males).<br>(nb: same sample as Bartley et al., 1997) | MZ: 31 (19–54)<br>DZ: 23 (18–29) | TB: 66%<br>LV: C 48% and E 50% GM subregions (>30) >50% heritability |

**Table 10.1** (continued)

| Brain area | Authors | Group size | Age (years) | Heritability |
|---|---|---|---|---|
| TB, GM, WM, cerebellum (CB), caudate (cau), putamen (put), thalamus (thal), cortical depth | White et al. (2002) | 12 MZ (6 males), 12 control pairs (6 males) no DZ | MZ: 24.5 ± 7.2<br>Cont: 24.4 ± 7.2 | MZ correlations:<br>CB, TB, GM, WM: $r > 0.90$<br>Cau, put, thal: $r > .75$ cort depth low correlations |
| Corpus callosum area | Scamvougeras et al. (2003) | 14 MZ, 12 DZ | Mean 27 years | 94% |
| White matter hyperintensities (WMH) | Atwood et al. (2004) | 1330 Individuals in genetically useful relationships | 60.99±9.61 | WMH: 55% |
| Longitudinal: genetic stability (4-year follow up). Corpus callosum (CC) and LV | Pfefferbaum et al. (2004) | 34 MZ, 37 DZ | T1:68–80 years<br>T2: 72–84 years | CC: a increase from 89 to 92%<br>LV: a decrease from 92 to 88%<br>New environmental influences |
| Density of focal brain gray and white matter. Parahippocampal gyrus | Hulshoff Pol et al. (2006)[#] | 54 MZ (33 males)<br>58 DZ (17 males, 21 OS)<br>34 sibs | MZM: 31.2, MZF: 34.1,<br>DZM: 30.3, DZF: 30.6,<br>OS: 30.3, sibs: 29 | occ-front-temp and white matter pathways: 76–85%<br>parahippocampal gyrus: 69% |

[*] Manual segmentation; [#]VBM; [$]midsagittal surface measurement; *NA*, not available.
MZ, monozygotic; DZ, dizygotic; MZM, monozygotic male; MZF, monozygotic female; DZM, dizygotic male; DZF, dizygotic female; OS, opposite sex; A, additive genetic; C, common environment; E, unique environment; FA, fractional anisotropy; GM, gray matter; WM, white matter; TB, total brain; IC, intracranial volume; occ-front-temp, occipito-fronto temporal.

subjects (Pfefferbaum et al., 2000; Pfefferbaum, Sullivan, & Carmelli, 2004).

A few studies have examined possible genetic effects on more specific brain areas. Volumes of frontal and temporal gray matter (GM) are particularly influenced by genetic factors (Thompson et al., 2001; Wright et al., 2002). Furthermore, brain density of the medial and superior frontal, superior temporal and occipital gray matter and connecting white matter of the superior occipito-frontal fasciculus and corpus callosum are particularly influenced by genetic factors (Hulshoff Pol et al., 2006).

Area measurements of the corpus callosum revealed heritability estimates between 79 and 94% (Pfefferbaum et al., 2000; Scamvougeras, Kigar, Jones, Weinberger, & Witelson, 2003). Variation in hippocampus volume was found to have a lower heritability with estimates of 40% (Sullivan, Pfefferbaum, Swan, & Carmelli, 2001) and 69% (Hulshoff Pol et al., 2006). Unique environmental factors influenced vast gray matter and white matter areas surrounding the lateral ventricles (up to 50%) (Hulshoff Pol et al., 2006).

In a study that did not include DZ twin pairs, MZ twin pair correlations were high ($>0.90$ for cerebellum, total brain, gray, and white matter and $>0.75$ for caudate nucleus, putamen, thalamus, and cortical depth) as compared to a healthy comparison group (White, Andreasen, & Nopoulos, 2002).

In the only study to date that measured heritability estimates of changes in brain volumes over time, genetic contributions to variability in intracranial volume, corpus callosum, and lateral ventricles were found to be high in healthy elderly (Pfefferbaum et al., 2000) remained high at longitudinal follow-up of 4 years (Pfefferbaum et al., 2004).

Next to twin studies, other designs can also be applied to yield estimates on genetic and environmental influences. For example, a family-based study reported heritability estimates of white matter hyperintensities of 55%. These estimates increased with age (Atwood et al., 2004).

In summary, human brain volume is considerably heritable. Moreover, it remains to be largely explained by genetic factors, even in old age. Individual variation in lateral ventricles is mainly explained by environmental factors, suggesting that surrounding brain tissue is at least partly influenced by environmental factors. Genetic effects were shown to vary regionally, with high heritabilities of frontal and temporal lobe volumes and densities, but moderate estimates in the hippocampus, and environmental influences on several medial brain areas. Areas that show high heritability for volume emphasize the relevance of these brain areas when searching for genes influencing brain structure.

It should be noted that only one longitudinal twin study is carried out in elderly subjects. Moreover, twin studies in children and/or adolescents are currently lacking. Therefore, no conclusions can be drawn about the stability of genetic influences on brain volume. Studies are under way to determine the influence of genetic and environmental factors on brain changes with age.

## Autosomal Genetic Abnormalities and Human Brain Morphology

### Huntington's Disease

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease, which is associated with increases in the length of a CAG triplet repeat present in a gene called "huntingtin" located on chromosome 4p16.3 (Rosas et al., 2001). Cognitively, HD patients suffer from attention impairments and problems with executive functioning as well as psychomotoric functions, whereas semantic memory and delayed recall memory seem to be intact (Ho et al., 2003).

Several MRI studies have demonstrated that, compared to healthy controls, HD is associated with global loss in volumes of total brain, total cerebrum, cerebral cortex (Table 10.2a) (Paulsen et al., 2006; Rosas et al., 2003). Also white matter reductions (Jernigan, Salmon, Butters, & Hesselink, 1991; Rosas et al., 2003) and cortical thinning (Rosas et al., 2005) have been reported. Focal atrophy in the basal ganglia is an often found abnormality in HD patients (Aylward et al., 1994, 1997, 1998, 2000, 2004; Beglinger et al., 2005; Fennema-Notestine et al., 2004; Harris et al., 1992; Jernigan et al., 1991; Kassubek, Juengling, et al., 2004; Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005; Kipps et al., 2005; Mascalchi et al., 2004; Paulsen et al., 2006; Peinemann et al., 2005; Rosas et al., 2001, 2003; Thieben et al., 2002). Other structures in HD that were smaller as compared to healthy subjects are the following: the hypothalamus (Kassubek, Juengling, et al., 2004), thalamus (Kassubek et al., 2005; Paulsen et al., 2006) amygdala, hippocampus, brainstem, cerebellum (Rosas et al., 2003), insula, dorsal midbrain (Thieben et al., 2002), and the frontal lobe (Aylward et al., 1998).

Interestingly, the major brain abnormality in HD, i.e., basal ganglia atrophy, was positively correlated with CAG repeat length, symptom severity (Aylward et al., 1997; Kassubek, Bernhard, et al., 2004; Rosas et al., 2001) as well as age of onset of the disease symptoms (Aylward et al., 1997).

In pre-clinical Huntington patients (who do not have symptoms yet, but who test positively for the "Huntingtin gene"), decreased volumes of the striatum, insula, and dorsal forebrain were detected when compared to healthy control subjects (Thieben et al., 2002). Furthermore, more progressive atrophy in the basal ganglia was found in clinical patients in a follow-up measurement as compared to pre-clinical patients (Kipps et al., 2005). Finally, striatal

**Table 10.2** Autosomal genetic diseases

| Syndrome | Brain area | Authors | Group size | Age (years) | p-Value/ES |
|---|---|---|---|---|---|
| **(a) Huntington's disease** | | | | | |
| | Total brain, total cerebrum, (GM and WM) ↓ | Rosas et al. (2003)* | HD: | 27–63 (34.8±10.41) | GM: $p<0.02$ |
| | | 18 HD, 18 HC | HC: matched | | WM: $p<0.0001$ |
| | | Paulsen et al. (2006)* | HD: 24 | HD: 36.8 (±9.7) | $P<0.001$ |
| | | | HC: 24 | HC: 36.6 (±9.1) | |
| | White matter ↓ | Jernigan et al. (1991)* | 11 HD | HD: 49±12.5 | $P<0.01$ |
| | | | 55 HC | HC: 54±14.1 | |
| | | Rosas et al. (2003)* | 18 HD, | HD: 27–63 | $P<0.0001$ |
| | | | 18 HC | (34.8±10.41) | |
| | | | | HC: matched | |
| | Cerebellum ↓ | Fennema-Notestine et al. (2004)* | 15 HD, | HD: 46.7 (±11.0) | WM: $p<0.001$ |
| | | | 22 HC | HC: 47.1 (±9.8) | GM: $p<0.01$ |
| | Basal ganglia ↓ | Jernigan et al. (1991) | 11 HD | HD: 49±12.5 | Caudate: $P=0.000$ |
| | | | 55 HC | HC: 54±14.1 | |
| | | Harris et al. (1992)*,[1] | 15 HD, | HD: 29–72 | Putamen: $P<0.000001$ |
| | | | 19 HC | (43.2±12.9) | Caudate: $P<0.004$ |
| | | | | HC: 23–73 | |
| | | | | (45.2±15.9) | |
| | | Aylward et al. (1994)* (tb not diff) | 10 HD+ 18 HD– | HD+: 34.4±5.44 | $P<0.001$ (total basal ganglia) |
| | | | | HD–: 39.72±8.99 | |
| | | Aylward et al. (1997)*,[2] Longitudinal | 23 HD | HD: 42.57±13.02 | $P<0.001$ (change) |
| | | | | Interval: 1.73 years | |
| | | Aylward et al. (1998)*,[1] | 20 HD (10 mild, 10 mod), | HD-mild: 44.8±15.4 | $P<0.004$ |
| | | | | HD-mod: 42.7±11.3 | |
| | | | 20 HC | HC-mild: 43.9±16 | |
| | | | | HC-mod: 42.6±11.5 | |
| | | Aylward et al. (2000)*,[1] | 30 HD | HD (total): 43.6 (±10.2) | $P<0.001$ |
| | | Aylward et al. (2004)*,[1] | 19 pre-HD, 17 HD | HD: 32.1(±6.6) | $P=0.05$ |
| | | | | HC: 32.5(±6.7) | |
| | | Rosas et al. (2001)* | 27 HD, 24 HC | HD: 25–63 | $P<0.0001$ |
| | | | | 43.8 (±10.3) | |
| | | | | HC: 29–62 | |
| | | | | 41.2 (±9.8) | |
| | | Rosas et al. (2003)*,[1] | 18 HD, 18 HC | HD: 27–63 | $P<0.0001$ |
| | | | | (34.8±10.41) | |
| | | | | HC: matched | |
| | | Thieben et al. (2002)# | 18 HD (from 34 tested) | HD–: 38.04±11.43 | Left-putamen: |
| | | | | HD+: 43.58±12.02 | $p=0.009$ |
| | | | | | Caud: $p=0.003$ |
| | | Kassubek et al. (2004b)# | 44 HD , 22 HC | HD: 23–66 44.7 (±10.7) | $P<0.001$ |
| | | | | HC: 25–68 44.1 (±16.9) | |
| | | Mascalchi et al. (2004) | 21 HD, 21 HC | HD: 58±11 | $P<0.001$ |
| | | | | HC: 54±13 | |

**Table 10.2** (continued)

| Syndrome | Brain area | Authors | Group size | Age (years) | p-Value/ES |
|---|---|---|---|---|---|
| | | Fennema-Notestine et al. (2004)*,1 | 15 HD, 22 HC | HD: 46.7 (±11.0)<br>HC: 47.1 (±9.8) | |
| | | Peinemann et al. (2005)# | 25 HD<br>25 HC | HD: 43.8 (±7.7)<br>HC: 42.9 (±9.8) | Caudate/putamen<br>$P<0.05$ |
| | | Paulsen et al. (2006)*,1 | HD: 24<br>HC: 24 | HD: 36.8 (±9.7)<br>HC: 36.6 (±9.1) | Cau: $p<0.002$<br>Put: $p<0.0001$ |
| | | Kipps et al. (2005) TBM Progression of atrophy | 17 HD+<br>13 HD– | HD+: 43.8 (±10.0)<br>HD–: 42.0 (±11.4) | $p<0.005$ |
| | | Beglinger et al. (2005)*,1 | 10 HD<br>10 HC | HD: 54.3 (±8.2)<br>HC: 53.9 (±9.0) | Cau: $p<0.0002$<br>Put: $p<0.0001$ |
| | | Kassubek et al. (2005)# | 44 HD, 22 | HD: 23–66 44.7 (±10.7)<br>HC: 25–68 44.1 (±16.9) | Cau and put: $p<0.001$ |
| | Thalamus ↓ | Kassubek et al. (2005)# 44 HD, 22 | HD: 23–66<br>44.7 (±10.7) | HC: 25–68<br>44.1 (±16.9) | $P<0.001$ |
| | | Paulsen et al. (2006)*,1 | HD: 24<br>HC: 24 | HD: 36.8 (±9.7)<br>HC: 36.6 (±9.1) | $p<0.019$ |
| | Hypothalamus ↓ | Kassubek et al. (2004b)# | 44 HD, 22 | HD: 23–66<br>44.7 (±10.7)<br>HC: 25–68<br>44.1 (±16.9) | $p<0.001$ |
| | Amygdala (amyg), hippocampus (hip), brainstem ↓ | Rosas et al. (2003)*,1 | 18 HD, 18 HC | HD: 27–63<br>(34.8±10.41)<br>HC: matched | Amyg: $p<0.001$<br>Hip: $p<0.01$<br>Brainstem: $p<0.0001$ |
| | Insula, dorsal midbrain ↓ | Thieben et al. (2002)# | 18 HD (from 34 tested) | HD–: 38.04±11.43<br>HD+: 43.58±12.02 | Insula:<br>R: $p<0.032$<br>L: $p<0.010$ |
| | Frontal lobe ↓ | Aylward et al. (1998)*,1 | 20 HD (10 mild, 10 mod),<br>20 HC | HD-mild: 44.8±15.4<br>HD-mod: 42.7±11.3<br>HC-mild: 43.9±16<br>HC-mod: 42.6±11.5 | *NA* |
| **(b) Down syndrome** | | | | | |
| | Cerebrum ↓ | Raz et al. (1995)* | 13 DS, 12 HC | DS: 22–50<br>(35.2±8.32)<br>HC: 23–49<br>(35.3±8.12) | $P<0.002$ |
| | | Weis et al. (1991)* (cerebral cortex) | 7 DS, 7 HC | DS: 30–45 (38)<br>HC: 36–44 (38) | $P=0.003$ |
| | Cerebellum ↓ | White et al. (2003)# | 19 DS, 11 HC | DS: 34–52<br>41.9(±6.0)<br>HC: 37–56<br>45.6(±6.1) | $P<0.05$ |
| | | Pinter et al. (2001a)*,1 | 16 DS, 15 HC | DS: 5–23.8<br>11.3 (±5.2)<br>HC: 5.4–23.2<br>11.9 (±4.7) | $P<0.0001$ |

**Table 10.2** (continued)

| Syndrome | Brain area | Authors | Group size | Age (years) | p-Value/ES |
|---|---|---|---|---|---|
| | | Raz et al. (1995)∗[3], | 13 DS, 12 HC | DS: 22–50 (35.2±8.32) HC: 23–49 (35.3±8.12) | $P<0.002$ |
| | | Jernigan et al. (1993)* | 6 DS, 21 HC | DS: 10–20 (15.5±3.4) HC: 10–24 (14.5±3.8) | $P<0.001$ |
| | | Weis et al. (1991)∗ | 7 DS, 7 HC | DS: 30–45 (38) HC: 36–44 (38) | $P = 0.05$ (controlled for TB: $p=0.06$) |
| | White matter ↓ | Weis et al. (1991)∗ | 7 DS, 7 HC | DS: 30–45 (38) HC: 36–44 (38) | $P=0.004$ |
| | Cingulate gyrus ↓ | White et al. (2003)[#] | 19 DS, 11 HC | DS: 34–52 41.9 (±6.0) HC: 37–56 45.6 (±6.1) | $P<0.05$ |
| | Amygdala ↔ | Pinter et al. (2001b)*,[1] | 16 DS, 15 HC | DS: 11.3 (±5.2) HC: 11.9 (±4.7) | R: $p<0.32$ L: $p<0.27$ |
| | Hippocampus ↓ | Pinter et al. (2001b)*,[1] | 16 DS, 15 HC | DS: 11.3 (±5.2) HC: 11.9 (±4.7) | R: $p<0.03$ L: $p<0.002$ |
| | | Raz et al. (1995)*,[3] | 13 DS, 12 HC | DS: 22–50 (35.2±8.32) HC: 23–49 (35.3±8.12) | $P<0.002$ |
| | | Kesslak et al. (1994)*,[2] | 13 DS, 10 HC | DS: 23–51 HC: matched | $P=0.0285$ |
| | | Teipel et al. (2003)*,[1] | 34 DS, 31 HC | DS: m: 41.6 years HC: 41.8 years | $P<0.001$ |
| | Corpus callosum ↓ (area) | Teipel et al. (2003)*,[1] | 34 DS, 31 HC | DS: m: 41.6 years HC: 41.8 years | $P=0.05$ |
| | Planum temporale ↓ | Frangou et al. (1997)*,[1] | 17 DS, 17 HC | DS: 39.2 (±8.7) HC: 39.5 (±9.1) | $P<0.0007$ |
| | Mammillary bodies ↓ | Raz et al. (1995)*,[3] | 13 DS, 12 HC | DS: 22–50 (35.2±8.32) HC: 23–49 (35.3±8.12) | $P<0.005$ |
| | Parahippocampal gyrus ↑ | White et al. (2003)[#] | 19 DS, 11 HC | DS: 34–52 41.9 (±6.0) HC: 37–56 45.6 (±6.1) | $P<0.05$ |
| | | Raz et al. (1995)*,[3] | 13 DS, 12 HC | DS: 22–50 (35.2±8.32) HC: 23–49 (35.3±8.12) | $P<0.008$ |
| | | Kesslak et al. (1994)*,[2] | 13 DS, 10 HC | DS: 23–51 HC: matched | $P=0.0022$ |
| | Parahippocampal gyrus ↓ | Teipel et al. (2004)[#] (with age) | 27 DS | DS: 41.1 (±9.1) | $P<0.05$ |
| | | Krasuski et al. (2002)*,[1] (with age) | 31 DS, 33 HC | DS: 41.6 (±9.1) HC: 41.6 (±10.7) | R: $p<0.04$ L: $p<0.009$ |

**Table 10.2** (continued)

| Syndrome | Brain area | Authors | Group size | Age (years) | p-Value/ES |
|---|---|---|---|---|---|
| **(c) Williams syndrome** | | | | | |
| | Total brain ↓ | Reiss et al. (2000)* | 14 WS, 14 HC | WS: 19–44 (28.7±8.9) HC: 20–48 (29.0±9.0) | $P<0.001$ |
| | | Schmitt et al. (2001a)*,[1] | 20 WS, 20 HC | WS: 19–44 28.5 (±8.3) HC: 19–48 28.5 (±8.2) | $P<0.001$ |
| | | Cherniske et al. (2004)* | 20 WS, Normative data comparison | WS: 30–51 38.8 | *NA* |
| | Cortical complexity ↑ | Thompson et al. (2005) | 42 WS 40 HC | WS: 29.2 (±9.0) HC27.5 (±7.4) | $p<0.0015$ |
| | Parieto-occipital sulcus ↓ | Meyer-Lindenberg et al. (2004)# | 13 WS, 11 HC | HC: 30.8 (±7.6) WS: 28.3 (±9.6) | $p<0.001$ |
| | | Boddaert et al. (2006)# | 9 WS 11 HC | WS: 11.6 (±3.1) HC: 11.8 (±2.2) | $p<0.05$ |
| | Intraparietal sulcus | Meyer-Lindenberg et al. (2004)# | 13 WS, 11 HC | WS: 28.3 (±9.6) HC: 30.8 (±7.6) | $p<0.001$ |
| | | Kippenhan et al. (2005) (sulcal depth) | 14 WS 13 HC | WS: 27.6 (±9.6) HC: 31.2 (±7.1) | $p<0.01$ |
| | Hypothalamus ↓ | Meyer-Lindenberg et al. (2004)# | 13 WS, 11 HC | WS: 28.3 (±9.6) HC: 30.8 (±7.6) | $p<0.001$ |
| | Superior and inferior parietal lobe ↓ | Eckert et al. (2005)*,[1] | 17 WS, 17 HC | WS: 28.9 HC: 27.1 | $p<0.05$ |
| | Occipital lobe and thalamus ↓ | Reiss et al. (2004)*,[1] | 43 WS. 40 HC | WS: 12–50 28.9 (±9.2) HC: 18–49 27.5 (±7.4) | Occ: $p<0.003$ Thal: $p<0.0001$ |
| | Corpus callosum ↓ | Tomaiuolo et al. (2002)*,[1] (corrected Talairach stereotaxic space) | 12 WS, 12 HC | WS-M: 13–20 20 (±7.2) WS-F: 13–20 16.6 (±3.01) HC-M: 13–29 20 (±6.9) HC-F: 13–19 16 (±3.46) | $p<0.015$ |
| | | Schmitt et al. (2001b) | 20 WS, 20 HC | WS: 19–44 28.5 (±8.3) HC: 19–48 28.5 (±8.2) | $p = 0.04$ |
| | Cerebellum ↑ | Jones et al. (2002) | 9 WS, 9 HC | WS: 0.6–3.5 (mean: 1.75) HC: 1.7–3.5 (mean: 2.42) | *NA* |

**Table 10.2** (continued)

| Syndrome | Brain area | Authors | Group size | Age (years) | p-Value/ES |
|---|---|---|---|---|---|
| | | Schmitt et al. (2001a)*,1 | 20 WS, 20 HC | WS: 19–44<br>28.5 (±8.3)<br>HC: 19–48<br>28.5 (±8.2) | $p<0.001$ |
| | | Reiss et al. (2000)*,1 | 14 WS, 14 HC | WS:19–44 (28.7±8.9)<br>HC: 20–48 (29.0±9.0) | $p<0.02$ |
| | | Wang et al. (1992)* | 11 WS, 18 HC | WS: 10–20 (14.7)<br>HC: 10–24 (15.4) | $p<0.05$ |
| | Amygdala (Am), orbito and orbitofrontal cortex (OFC), anterior cingulated (AC) and insular cortex ↑ | Reiss et al. (2004)*,1 | 43 WS. 40 HC | WS: 12–50<br>28.9 (±9.2)<br>HC: 18–49<br>27.5 (±7.4) | Am: $p<0.001$<br>AC: $p<0.005$<br>OFC: $p<0.0001$ |
| | Superior temporal gyrus ↑ | Reiss et al. (2000)*,1 | 14 WS, 14 HC | WS:19–44 (28.7±8.9)<br>HC: 20–48 (29.0±9.0) | $p=0.05$ |
| | | Reiss et al. (2004) | 43 WS, 43 HC | WS: 12–50<br>28.9 (±9.2)<br>HC: 18–49<br>27.5 (±7.4) | $p<.001$ |
| **(d) Velocardiofacial syndrome** | | | | | |
| | Total brain ↓ | Eliez et al. (2001a&b)* | 23 VCFS, 23 HC | 5.8–21.0<br>VC: 12.7(±3.9)<br>HC: 12.9(±4.1) | $P<0.0001$ |
| | | Simon et al. (2005)# | 18 VCFS<br>18 HC | VC: 7.3–14<br>9.88(±1.4)<br>HC: 7.5–14.1<br>10.42(±1.98) | $P<0.01$ |
| | | Kates et al. (2006)*,1 | 47 VCFS, 15 sibs, 18 HC | VC: 11.7 (±2.1),<br>sibs: 11.5 (± 1.8),<br>HC: 11.5 (±2.0) | $P<0.03$ |
| | WM>GM ↓ | Eliez et al. (2000)* | 15 VCFS, 15 HC | VC: 10.5(±3.1)<br>HC: 10.8(±2.7) | *NA* |
| | | Kates et al. (2001)* (non-frontal wm) | 10 VCFS, 10 HC | 7.9–14.5<br>VC: 10.1(±1.8)<br>HC: 10.1(±1.9) | $P<0.02$ |
| | | Simon et al. (2005) 18 VCFS | 18 HC<br>VC: 7.3–14 | 9.88(±1.4)<br>HC: 7.5–14.1 | 10.42(±1.98) *NA* |
| | | Campbell et al. (2006)# | 39 VCFS<br>26 HC | VC: 11 ± 3<br>HC: 11 ± 3 | $P<0.008$ |
| | Cerebellum ↓ | V Amelsvoort et al. (2004)#,*,1 | 12 VCFS (no schizos)<br>14 HC | VC: 31(±10)<br>HC: 36(±10) | $P<0.001$ |
| | | Eliez et al. (2001a)*,1 (lobules VI–VII) | 24 VCFS, 24 HC | VC: 12.5(±4)<br>HC: 12.7(±4.2) | $P<0.01$<br>Pons $P<0.0001$ |

**Table 10.2** (continued)

| Syndrome | Brain area | Authors | Group size | Age (years) | p-Value/ES |
|---|---|---|---|---|---|
| | | Campbell et al. (2006)[#] 39 VCFS | 26 HC<br>VC: 11 ± 3 | HC: 11 ± 3 | $P<0.008$ |
| | | Bish et al. (2006)[$] | 31 VCFS<br>23 HC | VC: 9 (±.9)<br>HC: 10 (±.6) | $P<0.013$ |
| | Hippocampus (hip), temporal lobe (tem), superior temporal gyrus (Sup) ↓ | Eliez et al. (2001b)[*,1]<br>(when controlled for TB: no difference!) | 23 VCFS, 23 HC | 5.8–21.0<br>VC: 12.7(±3.9)<br>HC: 12.9(±4.1) | Hip: $P<0.006$<br>Tem: $p<0.0001$<br>Sup: $p<0.02$ |
| | Left caudate nucleus ↓ (ratio r-cau:TB larger in controls!) | Sugama et al. (2000)[*,1] | 17 VC<br>15 HC | VC: 0.7–21<br>Mean: 5.41<br>HC: 1.1–25<br>Mean: 6.0 | $P<0.05$ |
| | Left parietal lobe ↓ | Eliez et al. (2000)[*,1] | 15 VCFS, 15 HC | VC: 10.5 (±3.1)<br>HC: 10.8 (±2.7) | $P<0.05$ |
| | FA frontal, parietal, and occipital lobe ↓ | Barnea-Goraly et al. (2003)[#](&dti) | 19 VCFS, 19 HC | 7.2–21.8<br>VC: 12.2 (±3.9)<br>HC: 14.4 (±4.2) | Right-midfrontal gyrus: $Z=5.07$ Left-superior parietal gyrus: $Z=3.7$ |
| | Posterior thalamus ↓ | Bish et al. (2004) | 18 VCFS<br>18 HC | VC: 9.8 (±1.4)<br>HC: 10.4 (±1.9) | $P < 0.031$ |
| | FA in corpus callosum ↓ | Simon et al. (2005)[#] | 18 VCFS<br>18 HC | VC: 7.3–14<br>9.88 (±1.4)<br>HC: 7.5–14.1<br>10.42 (±1.98) | $Z=4.74$ |
| | FA cingulate gyrus ↑ | Simon et al. (2005)[#] | 18 VCFS<br>18 HC | VC: 7.3–14<br>9.88 (±1.4)<br>HC: 7.5–14.1<br>10.42 (±1.98) | $Z=4.78$ |
| | Right and left amygdale ↑ | Kates et al. (2006)[*,1] | 47 VCFS, 15 sibs, 18 HC | VC: 11.7 (±2.1),<br>sibs: 11.5 (±1.8),<br>HC: 11.5 (±2.0) | Left: $p<0.002$<br>Right: $p<0.01$ |
| | Right caudate nucleus ↑ | Kates et al. (2004)<br>Campbell et al. (2006)[*,1] | 10 VCFS, 10 HC<br>39 VCFS<br>26 HC | *NA*<br>VC: 11 ± 3<br>HC: 11 ± 3 | *NA*<br>$P<0.04$ |
| | Frontal lobe (not wm) ↑ | Eliez et al. (2000)[*,1] | 15 VCFS,<br>15 HC | VC: 10.5 (±3.1)<br>HC: 10.8 (±2.7) | $P<0.001$ |
| | | Simon et al. (2005)[#] | 18 VCFS<br>18 HC | VC: 7.3–14<br>9.88 (±1.4)<br>HC: 7.5–14.1<br>10.42 (±1.98) | $Z = 5.1$ |

[*] Manual segmentation; [#] VBM; [$] midsagittal surface measurement; [1] controlled for total brain/intracranium; [2] no control TB/IC; [3] controlled for height
Abbreviations 2a–d: HD, Huntington's disease; DS, Down syndrome; WS, William's syndrome; VCFS, Velocardiofacial syndrome; HC, healthy controls; FA, fractional anisotropy; GM, gray matter; WM, white matter; TB, total brain; IC, intracranial volume

decline in pre-clinical HD patients was predictive of the time of occurrence of the first clinical symptoms (Aylward et al., 2004).

## Down Syndrome

Down syndrome (DS) is caused by a third copy of chromosome 21 (trisomy). DS is associated with mental retardation, and after the age of 40, individuals with DS suffer from cognitive decline or dementia (Lott & Head, 2001). A rapidly growing number of MRI studies have investigated brain atrophy in DS (Table 10.2b). When adult DS patients are compared to healthy subjects, they have smaller volumes of total cerebrum (Raz et al., 1995; Weis, Weber, Neuhold, & Rett, 1991), cerebellum (Jernigan & Bellugi, 1990; Raz et al., 1995; Weis et al., 1991; White, Alkire, & Haier, 2003), and total white matter (Weis et al., 1991). Regional decreases in volume in DS patients have been observed in the cingulate gyrus (White et al., 2003), hippocampus (Kesslak, Nagata, Lott, & Nalcioglu, 1994; Pinter, Brown, et al., 2001; Raz et al., 1995), planum temporale (Frangou et al., 1997), and mammillary bodies (Raz et al., 1995).

Cross-sectional studies carried out in DS patients show significantly more atrophy in patients than healthy controls with advancing age, mainly in the hippocampus (Krasuski, Alexander, Horwitz, Rapoport, & Schapiro, 2002; Teipel et al., 2003), amygdala (Krasuski et al., 2002), parahippocampal gyrus (Krasuski et al., 2002; Teipel et al., 2004), corpus callosum (Teipel et al., 2003), and frontal, parietal, and occipital gyrus (Teipel et al., 2004). However, in an earlier follow-up study no evidence was found for progressive changes in the hippocampus and amygdala of DS patients (Aylward et al., 1999).

Furthermore, children with DS also show brain abnormalities in the cerebellum (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993; Pinter, Eliez, Schmitt, Capone, & Reiss, 2001) and amygdala (Pinter, Brown, et al., 2001) compared to age-matched controls. When a direct distinction is made between DS children and adults, it appears that DS children already have a decreased volume of the cerebellum and hippocampus, although the amygdala and parietal gray matter seem to be preserved (Pinter, Eliez, et al., 2001).

When demented and non-demented DS patients are compared, demented DS patients show more pronounced atrophy with age (Pearlson et al., 1998). The amygdala showed no volumetric differences between demented and non-demented DS patients (Aylward et al., 1999).

A structure that has been reported to be enlarged in DS is the parahippocampal gyrus (Kesslak et al., 1994; Raz et al., 1995; White et al., 2003). Other studies, however, could not replicate this finding (Krasuski et al., 2002; Teipel et al., 2004).

## Williams Syndrome

Williams syndrome (WS) patients have a well-defined hemideletion on chromosome 7q11.23. WS patients are characterized by selective preservation of certain complex faculties (language, music, face processing, and sociability) in contrast to marked and severe deficits in nearly every other cognitive domain (Levitin et al., 2003).

Morphometric MRI studies have both investigated adult subjects as well as children and adolescents. In adults, studies demonstrated a decreased total brain volume in WS patients as compared to healthy control subjects (Table 10.2c) (Cherniske et al., 2004; Reiss et al., 2000; Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001a). Furthermore, taken the smaller total brain volume into account, reductions in parieto-occipital (Kippenhan et al., 2005; Meyer-Lindenberg et al., 2004) and intraparietal sulcus (Kippenhan et al., 2005; Meyer-Lindenberg et al., 2004), hypothalamus (Meyer-Lindenberg et al., 2004), superior parietal lobe (Eckert et al., 2005), gray matter of the occipital lobe, thalamus (Reiss et al., 2004), and corpus callosal area (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001b) were found.

Studies in WS children and adolescents showed reductions in parieto-occipital sulcus (Boddaert et al., 2006) and corpus callosal area (Tomaiuolo et al., 2002).

Some brain regions are found to be increased in WS adult patients when compared to healthy subjects. These include the cerebellum (Reiss et al., 2000; Schmitt et al., 2001a), amygdala, orbitofrontal and medial prefrontal cortex, anterior cingulate, insular cortex (Reiss et al., 2004), and superior temporal gyrus (Reiss et al., 2000, 2004). Furthermore, increased overall cortical complexity was found in WS (Thompson et al., 2005) as well as increased cortical gyrification in the right parietal and occipital lobes and in the left frontal lobe (Schmitt et al., 2002).

Enlargements in the cerebellum were found in WS infants (Jones et al., 2002) and adolescents (Wang, Hesselink, Jernigan, Doherty, & Bellugi, 1992).

In WS, as opposed to HD where one specific gene (i.e., the "huntingtin" gene) seems to be involved, only the locus of the deletion on the chromosome is known and knowledge of specific genes and their working mechanism(s) in the deleted region is scarce. Animal studies suggest involvement of the LIMK1-gene in abnormal brain development, which is located in the deleted region at chromosome 7q11.23 (Table 10.3) (Hoogenraad et al., 2002; Meng et al., 2002). Other genes mapped to region 7q11.23 and linked to abnormal brain development are CYLN2 (Hoogenraad et al., 1998), GTF21 (Danoff, Taylor, Blackshaw, & Desiderio, 2004; Morris et al., 2003), and WBSCR14 (Cairo, Merla, Urbinati, Ballabio, & Reymond, 2001).

**Table 10.3** Genes related to brain volumetric changes, discussed in this review[1]

| Brain area | Associated genes | Candidate genes | Disease | Gene map locus | Number of studies |
|---|---|---|---|---|---|
| Cerebral cortex (TB) | | ASPM*,** | Microcephaly | 1q31 | 3 |
| Prefrontal cortex, hippocampus | BDNF*,** | | | 11p13 | 4 |
| Prefrontal cortex | | COMT*,** | VCFS | 22q11.2 | 2 |
| Hippocampus | ApoE*,** | | | 19q13.2 | 10 |
| Limbic system, orbitofrontal cortex | MAOA*,** | | | Xp11.23 | 4 |
| Caudate nucleus | FOXP2*,** | | | 7q31 | 3 |
| Basal ganglia | | Huntingtin* | HD | 4p16.3 | 17 |
| Synaptic connections | | ProDH** | VCFS | 22q11.2 | 2 |
| Synaptic connections | | TBX1** | VCFS | 22q11.2 | 2 |
| Brain development | | LIMK1** | WS | 7q11.23 | 2 |
| | | CYLN2** | WS | 7q11.23 | 2 |
| | | WBSCR14** | WS | 7q11.23 | 1 |

[1] For references: see text
* Has been associated with brain volume changes in humans
** Has been associated with brain volume changes in animals
HD, Huntington's disease; DS, Down syndrome; WS, William's syndrome; VCFS, Velocardiofacial syndrome; TB, total brain volume

### Velocardiofacial Syndrome

Velocardiofacial syndrome (VCFS) is a neurogenetic disorder caused by deletions on chromosome 22q11.2. Patients with VCFS are characterized by learning disabilities (Swillen et al., 1999) and are often diagnosed with schizophrenia (Bassett et al., 2003; Murphy, Jones, & Owen, 1999).

Most of the structural MRI studies on VCFS are carried out in children and adolescents. In these studies, abnormalities have been found in several brain areas (Table 10.2d). A smaller total brain volume was reported (Eliez, Schmitt, White, & Reiss, 2000; Eliez, Schmitt, White, Wellis, & Reiss, 2001; Eliez, Blasey, et al., 2001; Simon et al., 2005) with (non-frontal) white matter relatively more affected than gray matter (Eliez et al., 2000; Kates et al., 2001; Simon et al., 2005; Campbell et al., 2006). More focal areas that appeared smaller in VCFS as compared to control subjects included the cerebellum (Bish et al., 2006), vermal lobules VI–VII, pons (Eliez, Schmitt, et al., 2001), temporal lobe, superior temporal gyrus, hippocampus (Eliez, Blasey, et al., 2001), left and right amygdala (Kates, Miller, et al., 2006), left caudate nucleus (Sugama et al., 2000), posterior thalamus (Bish, Nguyen, Ding, Ferrante, & Simon, 2004), and left parietal lobe (Eliez et al., 2000). Moreover, DTI studies investigating fractional anisotropy (FA) in white matter, an index of white matter coherence and integrity, found lower FA values in frontal, parietal, and temporal cortex, in connections between the frontal and temporal lobes (Barnea-Goraly et al., 2003) and corpus callosum (Simon et al., 2005). However, increased FA values were reported for the cingulate gyrus (Simon et al., 2005).

In the one study carried out in adult VCFS patients, a reduction in cerebellum density was found (van Amelsvoort et al., 2004). In the same study, adult VCFS patients with and without schizophrenia were compared. It was shown that VCFS patients with schizophrenia had larger ventricles and less overall white matter as compared to VCFS patients without schizophrenia (van Amelsfoort et al., 2004).

A brain area that is enlarged in VCFS is the right caudate nucleus (Kates et al., 2004; Campbell et al., 2006). Frontal lobe volumes seem to be relatively preserved (Eliez et al., 2000; Simon et al., 2005), although this does not seem to hold for the frontal white matter (Kates et al., 2004).

Similar to WS, in VCFS the locus of the deletion on the chromosome is known (22q11.2), but knowledge of specific genes and their working mechanism(s) in the deleted region is limited. Recently, the COMT (catechol-*O*-methyltransferase) low-activity genotype was identified as a risk factor for decline in prefrontal cortical volume (Gothelf et al., 2005). Furthermore, this finding showed an interaction with sex (Kates, Antshel, et al., 2006). In animal studies, the ProDH and TBX1 genes are also mapped to region 22q11 and are thought to be involved in refinement and stabilization of synaptic connections in the adolescent mouse brain (Rakic, Bourgeois, & Goldman-Rakic, 1994).

## Other Genetic Approaches

Next to studying brain volume in specific genetic abnormalities, there are other genetic approaches that may elucidate genes involved in brain variation. These include studying the brains of families with a particular genetic makeup, searching for genes in subjects with brain morphological abnormalities, and associating brain volumes with genetic polymorphisms in candidate genes in healthy subjects.

In the so-called "KE family", half the family in three generations is affected by a severe speech and language disorder, which is transmitted as an autosomal-dominant monogenic trait (Vargha-Khadem, Watkins, Alcock, Fletcher, & Passingham, 1995). Genetic linkage studies identified a

locus, designated SPCH1, on chromosome 7q31 (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998). A point mutation was identified in the affected family members which alters an invariant amino acid residue in the DNA-binding domain of a forkhead/winged helix transcription factor, encoded by the gene FOXP2 (Table 10.3) (Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001). The affected family members have a reduction in volume of the caudate nucleus bilaterally, as well as changes in gray matter in other mostly motor- and speech-related brain areas, as compared to the unaffected members and healthy control subjects (Watkins et al., 2002). The discovery of the responsible gene in the "KE family" led to further research into the FOXP2 gene and its role in brain development. For example, the expression pattern of the FOXP2 mRNA has been found in the developing brain of mouse (Ferland, Cherry, Preware, Morrisey, & Walsh, 2003; Lai, Gerrelli, Monaco, Fisher, & Copp, 2003) and human, including the basal ganglia, thalamus, and cerebellum (Lai et al., 2003).

The search for genes in subjects with particular morphological changes in the brain was successful in autosomal recessive primary microcephaly (MCPH). MCPH is characterized by shrinkage of nearly 70% of the cortex. Involvement of the ASPM gene (Bond et al., 2002; Mekel-Bobrov et al., 2005) and the microcephalin gene (MCPH1) (Evans et al., 2004) was suggested in the determination of cerebral cortex size. The ASPM gene is the human ortholog (i.e., evolved from) of the *Drosophila melanogaster* abnormal spindle gene (asp), which is essential for normal mitotic spindle function in embryonic brain development. Mutations in the ASPM gene associated with MCPH suggest that regulation of mitotic spindle orientation may be an important evolutionary mechanism controlling brain size. However, in healthy subjects, recently no associations of allelic variants of the ASPM gene and MCPH1 gene and total brain volume were found (Woods et al., 2006). It was argued that outside the context of the microcephalic state, it is misleading to refer to the ASPM gene and/or MCPH1 as regulating or controlling brain size (Woods et al., 2006).

Another genetic approach that may elucidate genes involved in brain variation is studying polymorphisms of specific genes in healthy subjects. A polymorphism is defined as the existence of multiple alleles of a gene within a population. It is a naturally occurring variation in the sequence of genetic information on a segment of DNA among individuals. Those variations are considered normal (not to be confused with true mutations, which are alterations of the original genetic material, often being harmful).

The few studies on polymorphisms in healthy subjects have revealed associations with brain volumes or densities. For example, Val/met (i.e., valine/methionine amino acids) variant carriers of the brain-derived neurotrophic factor (BDNF) gene (a gene involved in reducing the amount of naturally occurring neuronal cell death) were found to have a reduced size of the prefrontal cortex (Pezawas et al., 2004) and hippocampus compared to val/val carriers (Bueller et al., 2006; Pezawas et al., 2004; Szeszko et al., 2005). In addition, in met-BDNF carriers a negative relation was found between dorsolateral prefrontal cortex volume and age, which was not present in the val-BDNF carriers (Nemoto et al., 2006).

A study of allelic variants of the apolipoprotein (ApoE) gene – thought to be involved in cell growth and regeneration of nerves – showed that healthy elderly subjects who were homozygous for the Epsilon4 allele, i.e., e4-e4 genotype had smaller hippocampal volumes than subjects heterozygous for that allele and than e4 non-carriers (Lemaitre et al., 2005; Lind et al., 2006). Also, the presence of a single ApoE-epsilon4 allele is associated with an increased rate of hippocampal volume loss in healthy women (Cohen, Small, Lalonde, Friz, & Sunderland, 2001).

Two variants of the X-linked monoamine oxidase A gene (MAOA) were recently associated with brain volumes in healthy subjects. The low expression variant predicted volume reductions in cingulate gyrus, amygdala, insula, and hypothalamus, whereas the high expression variant was associated with changes in orbitofrontal volume (Meyer-Lindenberg et al., 2006).

Studies of polymorphisms and brain volumetric variation in psychiatric populations also found genes associated with alterations in brain volume. For example, in schizophrenia, a reduction in BDNF production and availability in the dorsolateral prefrontal cortex (DLPFC) was found (Weickert et al., 2003). Furthermore, the disrupted-in-schizophrenia 1 (DISC1) gene was associated with prefrontal gray matter loss (Cannon et al., 2005) and hippocampus decrease (Callicott et al., 2005).

In a study on attention-deficit hyperactivity disorder (ADHD) it was shown that homozygosity for the 10R-allele of the dopamine transporter 1 (DAT1) gene was associated with smaller caudate nucleus volumes and homozygosity of 4R-allele of the dopamine receptor D4 (DRD4) gene with smaller prefrontal gray matter (Durston et al., 2005).

Overall, studying polymorphisms in healthy subjects yields valuable information on specific genes that may be involved in brain volume. However, as it is a newly developing area of research, the robustness of the findings needs to be pointed out and therefore replication is warranted.

## Discussion and Conclusion

In this chapter, the influences of genes on human brain volume were reviewed. For this purpose, twin studies were included to assess the heritability of human brain volumetric

variation in the general population. In addition, brain structures in patients with a clear genetic etiology were reviewed. Finally, other genetic approaches to the search of genes involved in brain volume were discussed. These other approaches included studies on brain volumes of families with a particular genetic makeup, studies that search for genes in subjects with brain morphological abnormalities, and studies examining genetic polymorphisms in healthy subjects.

Twin studies showed high heritability estimates for specific brain structures and for overall brain size in adulthood (between 66 and 97%). Both global gray and global white matter are largely determined by genes. However, individual variation in lateral ventricles is mainly explained by environmental factors, suggesting that surrounding brain tissue is at least partly influenced by environmental factors. Genetic effects were shown to vary regionally, with high heritability estimates of frontal lobe volumes (90–95%), but moderate estimates of the hippocampus (40–69%), and environmental influences on several medial brain areas. Areas that show a high heritability for volume emphasize the relevance of these brain areas when searching for genes influencing brain structure. For focal structures heritability estimates differ, suggesting that different genes influence focal brain structures differentially.

The study of diseases with a clear genetic etiology yielded specific information on changes in brain volumes, densities, and fractional anisotropy. In patients with Huntington's disease, decreased volumes of the basal ganglia were found. Moreover, age at onset of the first symptoms was significantly related to the amount of atrophy in the basal ganglia. Also, the larger the CAG repeat length in Huntington's disease, the more atrophy in the basal ganglia was found. In Down syndrome, a decreased cerebellum and increased parahippocampal gyrus volume and density were found. In Williams syndrome, an increased amygdala, superior temporal gyrus, and cerebellum were reported. Finally in Velocardiofacial syndrome a decreased parietal lobe volume was found. Interestingly, across all disorders, pronounced decreases in white matter volume and hippocampus volume were revealed, irrespective of the genes and/or chromosomes involved. Furthermore, in all brain imaging studies of autosomal abnormalities, a decreased total brain volume was consistently found. It must be noted that although most studies found decreases in brain volume associated with autosomal abnormalities, there are also genetic disorders in which an enlarged brain is present. These include Sotos syndrome (haplo-insufficiency of the NSD1 gene on 5q35) (Kurotaki et al., 2002), also known as cerebral gigantism. However, no quantitative MRI studies in Sotos syndome have been carried out, and therefore these data were not included in this review.

Results of other genetic approaches, such as investigating allelic variation in the healthy population, have revealed information on specific genes that may be involved in human brain volume. Polymorphisms of the brain-derived neurotrophic factor (BDNF) and apolipoprotein (ApoE) genes have been associated with prefrontal cortex and hippocampus volumes. More specifically, met-BDNF carriers showed reduced prefrontal cortex and hippocampus volumes compared to val-BDNF carriers. Homozygous carriers of the Epsilon 4-allele showed smaller hippocampus volumes than heterozygous carriers. In addition, high- and low-expression variants of the monoamine oxidase A gene (MAOA) resulted in structural differences in limbic and frontal areas. The study of polymorphisms in healthy subjects is a rapidly developing area of research which allows direct investigation of genetic influence (not confounded by disease).

Establishing the extent to which brain morphology is influenced by genes (and environment) contributes both to our understanding of healthy functioning as well as to elucidating the causes of brain disease. More specifically, it enhances our knowledge of individual variation in brain functioning and facilitates the interpretation of the morphological changes found in psychiatric disorders such as schizophrenia. Also, it allows future efforts to find particular genes responsible for brain structures to be concentrated in areas that are under considerable genetic influence (Hulshoff Pol et al., 2006).

Taken together, studies have shown that adult human brain volume is highly genetically determined. Since brain volume changes dynamically throughout life, longitudinal twin studies in childhood as well as in adulthood are needed to investigate the stability of genetic (and environmental) influences. During different age ranges, genes may exert different effects. Studies carried out in autosomal pathologies were reviewed to search for genes or chromosomal regions which are involved in volumetric changes. The genes that have been discovered in these areas might serve as a model for the genes being implicated in healthy individuals; however, direct evidence of the influence of specific genes on the (maintenance of) human brain volume (throughout life) is currently lacking. Polymorphism research on these candidate genes might be helpful in enhancing our knowledge on their influence in healthy human brain volume.

There are a number of limitations to the reviewed approaches of studying genes involved in human brain volume. These limitations need to be taken into account when interpreting findings of studies into the genes involved in human brain structure. First, it must be noted that twin studies in children and adolescents have not been carried out so far. Therefore, no conclusions can be drawn as to the genetic influences on brain volume during childhood. Moreover, only one longitudinal MRI study in twins pairs (in older adults) was completed up to now, and therefore conclusions as to the stability of genetic influences onto brain volume throughout life await further study. Furthermore, it has been argued

that the twin method may yield an inflated estimation of heritabilities compared to family and/or adoption studies. On the other hand, family studies might give lower heritability estimations as different ages within families are compared (for a discussion on this topic, see Martin, Boomsma, & Machin, 1997).

Limitations in studying genetic disorders include the presence of co-morbidity in some disorders. In Down syndrome patients who also suffer from dementia, global volumetric reductions are more pronounced with age and particularly present in the amygdala. Also, in Velocardiofacial patients diagnosed with schizophrenia larger ventricles and less white matter are found as compared to Velocardiofacial patients without schizophrenia. However, this finding does not necessarily mean that reductions in white matter results from genetic expression associated with brain morphology. In Velocardiofacial, the reduction of (the integrity of) white matter may well be a secondary to the vascular risk of these patients, i.e., heart defects. Vascular risk factors have been related to white matter lesions (de Leeuw et al., 2004; DeCarli et al., 2005). A second limitation includes the possible confounding effects of the pathology on brain volume. For example, it can be argued that being in a disadvantageous environment (a disease–environment interaction) might lead to decreases in brain morphology. However, brain volumetric changes can be directly associated with the genetic abnormality, which is suggested in Huntington's disease: decreased caudate nucleus volumes were reported prior to disease onset in subjects having the mutation in the huntingtin gene (Thieben et al., 2002). Here, it is important to mention that while Huntington's disease is the only neurodegenerative disorder discussed in this chapter, it offers valuable information on the effects of a single gene in subjects with and without having symptoms. Third, the relative small number of subjects usually involved in the studies may have limited its statistical power. Fourth, different types of medication of the subjects might have confounded the results. For example, Huntington's disease patients often use antipsychotics and/or antidepressants (Bonelli, Wenning, & Kapfhammer, 2004), which have been found to affect brain morphology (Bremner & Vermetten, 2004; Lieberman et al., 2005). Fifth, it is difficult to form a well-matched control group to diseases as Down syndrome, where mental retardation should be taken into account. A limitation in the section of polymorphism studies is that psychiatric and neurological disorders such as Alzheimer's disease and schizophrenia were not discussed in this paper. These conditions can also give more insight into the genetic mechanisms influencing brain volume.

Finally, a limitation which applies to all the reviewed studies is the MRI methodology. Intracranial or total brain volume was not always corrected for, which limits conclusions regarding the influence of a particular gene on small brain structures. Also, methodology of quantification of small structures in the brain can differ across the reviewed studies. For instance, manual segmentation of a structure versus region-of-interest (ROI) analysis with voxel-based morphometry might not lead to completely overlapping findings.

## Future Directions

The studies that were discussed in this review have revealed several genes to be associated with the regulation of human brain structure. However, at this point it seems too early to draw general conclusions about which genes are implicated in human brain morphology. Future studies, with other genetic approaches and new MRI methodology may enhance our understanding of the genes involved in human brain structure.

Without specific knowledge of candidate genes, linkage studies are now employed with the goal to localize a gene that influences a phenotype. This approach can be used when genetic marker data (based on DNA polymorphisms of known location in the genome) are available in extended families or in sibling pairs. Linkage studies are often called a theoretical ("blind" search for genes) in contrast to association studies which require knowledge of candidate genes (Vink & Boomsma, 2002). Linkage studies require data collection in related individuals (e.g., siblings or large pedigrees). Also, if the location of a certain polymorphism is not known, a linkage study of the whole genome can be carried out. To our knowledge, only one genome-wide linkage study in healthy subjects has been performed, in relation to brain volume. For white matter hyper-intensity volumes one linkage peak was identified on chromosome 4p (DeStefano et al., 2006). This is the region where the gene responsible for Huntington's disease, i.e., huntingtin, is located. The area of genome-wide research deserves further study as it allows identifying candidate genes involved in human brain volume.

A newly emerging field of genetic research is the study of epigenetics. Epigenetics comprises mechanisms of inheritance, which are not the consequences of changes in DNA structure. They affect gene transcription with environmental factors acting as modulators or inducers of epigenetic factors. One such (important) factor is DNA methylation (see Santos, Mazzola, & Carvalho, 2005 for a review on the working mechanisms). The genome-wide pattern of DNA methylation was found to be more alike within monozygotic young than in monozygotic adult and elderly twin pairs (Fraga et al., 2005). It is therefore important to investigate which environmental factors have an influence on the expression of genes (as found in DNA methylation). Consequently, the study of interaction between genes and environmental factors is warranted. Furthermore, the simultaneous effects of

multiple genes and possibly the interaction among genes, also need investigation as one could argue that a single gene polymorphism cannot explain morphological changes in the brain.

New brain imaging methods, such as diffusion tensor imaging (DTI)-fiber tracking, allow study of the connections and/or coherence of white matter fibers. Since white matter was found to be affected in most genetic diseases, future attention could therefore be focused on genes involved in neural networks. Considering the changes in brain structure throughout development in both childhood and adulthood, the study of genes involved in the plasticity of brain structure throughout life is warranted. Indeed, longitudinal studies in (pre)adolescent twin pairs and their siblings are underway to study these effects (Peper et al., 2004).

In summary, it can be concluded that adult human brain volume is highly determined by genetic factors. Specific genes have already been associated with volumes of several brain structures. Particularly white matter and hippocampus volumes are associated with a number of these candidate genes. Many more genes and their interaction with environmental factors that are involved in brain volume in childhood, adolescence, and adulthood are expected to be found in the coming years.

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## References

Atwood, L. D., Wolf, P. A., Heard-Costa, N. L., Massaro, J. M., Beiser, A., D'Agostino, R. B., et al. (2004). Genetic variation in white matter hyperintensity volume in the Framingham Study. *Stroke, 35*, 1609–1613.

Aylward, E. H., Brandt, J., Codori, A. M., Mangus, R. S., Barta, P. E., & Harris, G. J. (1994). Reduced basal ganglia volume associated with the gene for Huntington's disease in asymptomatic at-risk persons. *Neurology, 44*, 823–828.

Aylward, E. H., Li, Q., Stine, O. C., Ranen, N., Sherr, M., Barta, P. E., et al. (1997). Longitudinal change in basal ganglia volume in patients with Huntington's disease. *Neurology, 48*, 394–399.

Aylward, E. H., Anderson, N. B., Bylsma, F. W., Wagster, M. V., Barta, P. E., Sherr, M., et al. (1998). Frontal lobe volume in patients with Huntington's disease. *Neurology, 50*, 252–258.

Aylward, E. H., Li, Q., Honeycutt, N. A., Warren, A. C., Pulsifer, M. B., Barta, P. E., et al. (1999). MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. *American Journal of Psychiatry, 156*, 564–568.

Aylward, E. H., Codori, A. M., Rosenblatt, A., Sherr, M., Brandt, J., Stine, O. C., et al. (2000). Rate of caudate atrophy in presymptomatic and symptomatic stages of Huntington's disease. *Movement Disorders, 15*, 552–560.

Aylward, E. H., Sparks, B. F., Field, K. M., Yallapragada, V., Shpritz, B. D., Rosenblatt, A., et al. (2004). Onset and rate of striatal atrophy in preclinical Huntington disease. *Neurology, 63*, 66–72.

Baaré, W. F., Hulshoff Pol, H. E., Boomsma, D. I., Posthuma, D., de Geus, E. J., Schnack, H. G., et al. (2001). Quantitative genetic modeling of variation in human brain morphology. *Cerebral Cortex, 11*, 816–824.

Barnea-Goraly, N., Menon, V., Krasnow, B., Ko, A., Reiss, A., & Eliez, S. (2003). Investigation of white matter structure in velocardiofacial syndrome: a diffusion tensor imaging study. *American Journal of Psychiatry, 160*, 1863–1869.

Bartley, A. J., Jones, D. W., & Weinberger, D. R. (1997). Genetic variability of human brain size and cortical gyral patterns. *Brain, 120*(Pt 2), 257–269.

Bartzokis, G., Beckson, M., Lu, P. H., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Archives of General Psychiatry, 58*, 461–465.

Bassett, A. S., Chow, E. W.C., AbdelMalik, P., Gheorghiu, M., Husted, J., & Weksberg, R. (2003). The schizophrenia phenotype in 22q11 deletion syndrome. *American Journal of Psychiatry, 160*, 1580–1586.

Beglinger, L. J., Nopoulos, P. C., Jorge, R. E., Langbehn, D. R., Mikos, A. E., Moser, D. J., et al. (2005). White matter volume and cognitive dysfunction in early Huntington's disease. *Cognitive and Behavioral Neurology, 18*, 102–107.

Bish, J. P., Nguyen, V., Ding, L., Ferrante, S., & Simon, T. J. (2004). Thalamic reductions in children with chromosome 22q11.2 deletion syndrome. *Neuroreport, 15*, 1413–1415.

Bish, J. P., Pendyal, A., Ding, L., Ferrante, H., Nguyen, V., Donald-McGinn, D., et al. (2006). Specific cerebellar reductions in children with chromosome 22q11.2 deletion syndrome. *Neuroscience Letters, 399*, 245–248.

Boddaert, N., Mochel, F., Meresse, I., Seidenwurm, D., Cachia, A., Brunelle, F., et al. (2006). Parieto-occipital grey matter abnormalities in children with Williams syndrome. *Neuroimage, 30*, 721–725.

Bond, J., Roberts, E., Mochida, G. H., Hampshire, D. J., Scott, S., Askham, J. M., et al. (2002). ASPM is a major determinant of cerebral cortical size. *Nature Genetics, 32*, 316–320.

Bonelli, R. M., Wenning, G. K., & Kapfhammer, H. P. (2004). Huntington's disease: present treatments and future therapeutic modalities. *International Clinical Psychopharmacology, 19*, 51–62.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3*, 872–882.

Bremner, J. D., & Vermetten E. (2004). Neuroanatomical changes associated with pharmacotherapy in posttraumatic stress disorder. *Biobehavioral Stress Response: Protective and Damaging Effects, 1032*, 154–157.

Bueller, J. A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., & Zubieta, J. K. (2006). BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biological Psychiatry, 59*, 812–815.

Cairo, S., Merla, G., Urbinati, F., Ballabio, A., & Reymond A. (2001). WBSCR14, a gene mapping to the Williams–Beuren syndrome deleted region, is a new member of the Mlx transcription factor network. *Human Molecular Genetics, 10*, 617–627.

Callicott, J. H., Straub, R. E., Pezawas, L., Egan, M. F., Mattay, V. S., Hariri, A. R., et al. (2005). Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia.*Proceedings of the National Academy of Sciences of the United States of America, 102*, 8627–8632.

Campbell, L. E., Daly, E., Toal, F., Stevens, A., Azuma, R., Catani, M., et al. (2006). Brain and behaviour in children with 22q11.2 deletion syndrome: A volumetric and voxel-based morphometry MRI study. *Brain, 129*, 1218–1228.

Cannon, T. D., Hennah, W., van Erp, T. G., Thompson, P. M., Lonnqvist, J., Huttunen, M., et al. (2005). Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and

impaired short- and long-term memory. *Archives of General Psychiatry, 62*, 1205–1213.

Carmelli, D., DeCarli, C., Swan, G. E., Jack, L. M., Reed, T., Wolf, P. A., et al. (1998). Evidence for genetic variance in white matter hyperintensity volume in normal elderly male twins. *Stroke, 29*, 1177–1181.

Carmelli, D., Reed, T., & DeCarli C. (2002). A bivariate genetic analysis of cerebral white matter hyperintensities and cognitive performance in elderly male twins. *Neurobiology of Aging, 23*, 413–420.

Cherniske, E. M., Carpenter, T. O., Klaiman, C., Young, E., Bregman, J., Insogna, K., et al. (2004). Multisystem study of 20 older adults with Williams syndrome. *American Journal of Medical Genetics, 131A*, 255–264.

Cohen, R. M., Small, C., Lalonde, F., Friz, J., & Sunderland T. (2001). Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. *Neurology, 57*, 2223–2228.

Danoff, S. K., Taylor, H. E., Blackshaw, S., & Desiderio S. (2004). TFII-I, a candidate gene for Williams syndrome cognitive profile: Parallels between regional expression in mouse brain and human phenotype. *Neuroscience, 123*, 931–938.

de Leeuw, F. E., Richard, F., de Groot, J. C., van Duijn, C. M., Hofman, A., van Gijn, J., et al. (2004). Interaction between hypertension, apoE, and cerebral white matter lesions. *Stroke, 35*, 1057–1060.

DeCarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M., Au, R., et al. (2005). Measures of brain morphology and infarction in the Framingham heart study: establishing what is normal. *Neurobiology of Aging, 26*, 491–510.

DeStefano, A. L., Atwood, L. D., Massaro, J. M., Heard-Costa, N., Beiser, A., Au, R., et al. (2006). Genome-wide scan for white matter hyperintensity: The Framingham Heart Study. *Stroke, 37*, 77–81.

Durston, S., Fossella, J. A., Casey, B. J., Hulshoff Pol, H. E., Galvan, A., Schnack, H. G., et al. (2005). Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Molecular Psychiatry, 10*, 678–685.

Eckert, M. A., Leonard, C. M., Molloy, E. A., Blumenthal, J., Zijdenbos, A., & Giedd, J. N. (2002). The epigenesis of planum temporale asymmetry in twins. *Cerebral Cortex, 12*, 749–755.

Eckert, M. A., Hu, D., Eliez, S., Bellugi, U., Galaburda, A., Korenberg, J., et al. (2005). Evidence for superior parietal impairment in Williams syndrome. *Neurology, 64*, 152–153.

Eliez, S., Schmitt, J. E., White, C. D., & Reiss, A. L. (2000). Children and adolescents with velocardiofacial syndrome: a volumetric MRI study. *American Journal of Psychiatry, 157*, 409–415.

Eliez, S., Blasey, C. M., Schmitt, E. J., White, C. D., Hu, D., & Reiss, A. L. (2001). Velocardiofacial syndrome: are structural changes in the temporal and mesial temporal regions related to schizophrenia? *American Journal of Psychiatry, 158*, 447–453.

Eliez, S., Schmitt, J. E., White, C. D., Wellis, V. G., & Reiss, A. L. (2001). A quantitative MRI study of posterior fossa development in velocardiofacial syndrome. *Biological Psychiatry, 49*, 540–546.

Evans, P. D., Anderson, J. R., Vallender, E. J., Gilbert, S. L., Malcom, C. M., Dorus, S., et al. (2004). Adaptive evolution of ASPM, a major determinant of cerebral cortical size in humans. *Human Molecular Genetics, 13*, 489–494.

Fennema-Notestine, C., Archibald, S. L., Jacobson, M. W., Corey-Bloom, J., Paulsen, J. S., Peavy, G. M., et al. (2004). In vivo evidence of cerebellar atrophy and cerebral white matter loss in Huntington disease. *Neurology, 63*, 989–995.

Ferland, R. J., Cherry, T. J., Preware, P. O., Morrisey, E. E., & Walsh, C. A. (2003). Characterization of Foxp2 and Foxp1 mRNA and protein in the developing and mature brain. *Journal of Comparative Neurology, 460*, 266–279.

Fisher, S. E., Vargha-Khadem, F., Watkins, K. E., Monaco, A. P., & Pembrey, M. E. (1998). Localisation of a gene implicated in a severe speech and language disorder. *Nature Genetics, 18*, 168–170.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestart, M. L., et al. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 10604–10609.

Frangou, S., Aylward, E., Warren, A., Sharma, T., Barta, P., & Pearlson G. (1997). Small planum temporale volume in Down's syndrome: a volumetric MRI study. *American Journal of Psychiatry, 154*, 1424–1429.

Gale, C.R., O'Callaghan, F. J., Bredow, M., & Martyn, C. N. (2006). The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. *Pediatrics, 118*, 1486–1492.

Geschwind, D. H., Miller, B. L., DeCarli, C., & Carmelli D. (2002). Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 3176–3181.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., et al. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience, 2*, 861–863.

Gogtay, N., Nugent, T. F., III, Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., et al. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus, 16*, 664–672.

Gothelf, D., Eliez, S., Thompson, T., Hinard, C., Penniman, L., Feinstein, C., et al. (2005). COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nature Neuroscience, 8*, 1500–1502.

Harris, G. J., Pearlson, G. D., Peyser, C. E., Aylward, E. H., Roberts, J., Barta, P. E., et al. (1992). Putamen volume reduction on magnetic resonance imaging exceeds caudate changes in mild Huntington's disease. *Annals of Neurology, 31*, 69–75.

Ho, A. K., Sahakian, B. J., Brown, R. G., Barker, R. A., Hodges, J. R., Ane, M. N., et al. (2003). Profile of cognitive progression in early Huntington's disease. *Neurology, 61*, 1702–1706.

Hoogenraad, C. C., Eussen, B. H., Langeveld, A., van Haperen, R., Winterberg, S., Wouters, C. H., et al. (1998). The murine CYLN2 gene: genomic organization, chromosome localization, and comparison to the human gene that is located within the 7q11.23 Williams syndrome critical region. *Genomics, 53*, 348–358.

Hoogenraad, C. C., Koekkoek, B., Akhmanova, A., Krugers, H., Dortland, B., Miedema, M., et al. (2002). Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. *Nature Genetics, 32*, 116–127.

Hulshoff Pol, H. E., Posthuma, D., Baare, W. F., de Geus, E. J., Schnack, H. G., van Haren, N. E., et al. (2002). Twin-singleton differences in brain structure using structural equation modelling. *Brain, 125*, 384–390.

Hulshoff Pol, H. E., Schnack, H. G., Posthuma, D., Mandl, R. C.W., Baare, W. F., van Oel, C., et al. (2006). Genetic contributions to human brain morphology and intelligence. *Journal of Neuroscience, 40*, 10235–10242.

Jernigan, T. L., & Bellugi U. (1990). Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. *Archives of Neurology, 47*, 529–533.

Jernigan, T. L., Salmon, D. P., Butters, N., & Hesselink, J. R. (1991). Cerebral structure on MRI, Part II: Specific changes in Alzheimer's and Huntington's diseases. *Biological Psychiatry, 29*, 68–81.

Jernigan, T. L., Bellugi, U., Sowell, E., Doherty, S., & Hesselink, J. R. (1993). Cerebral morphologic distinctions between Williams and Down syndromes. *Archives of Neurology, 50*, 186–191.

Jones, W., Hesselink, J., Courchesne, E., Duncan, T., Matsuda, K., & Bellugi U. (2002). Cerebellar abnormalities in infants and toddlers

with Williams syndrome. *Developmental Medicine and Child Neurology, 44*, 688–694.

Kassubek, J., Bernhard, L. G., Ecker, D., Juengling, F. D., Muche, R., Schuller, S., et al. (2004). Global cerebral atrophy in early stages of Huntington's disease: Quantitative MRI study. *Neuroreport, 15*, 363–365.

Kassubek, J., Juengling, F. D., Kioschies, T., Henkel, K., Karitzky, J., Kramer, B., et al. (2004). Topography of cerebral atrophy in early Huntington's disease: A voxel based morphometric MRI study. *Journal of Neurology Neurosurgery and Psychiatry, 75*, 213–220.

Kassubek, J., Juengling, F. D., Ecker, D., & Landwehrmeyer, G. B. (2005). Thalamic atrophy in Huntington's disease co-varies with cognitive performance: A morphometric MRI analysis. *Cerebral Cortex, 15*, 846–853.

Kates, W. R., Burnette, C. P., Jabs, E. W., Rutberg, J., Murphy, A. M., Grados, M., et al. (2001). Regional cortical white matter reductions in velocardiofacial syndrome: A volumetric MRI analysis. *Biological Psychiatry, 49*, 677–684.

Kates, W. R., Burnette, C. P., Bessette, B. A., Folley, B. S., Strunge, L., Jabs, E. W., et al. (2004). Frontal and caudate alterations in velocardiofacial syndrome (deletion at chromosome 22q11.2). *Journal of Child Neurology, 19*, 337–342.

Kates, W. R., Antshel, K. M., Abdulsabur, N., Colgan, D., Funke, B., Fremont, W., et al. (2006). A gender-moderated effect of a functional COMT polymorphism on prefrontal brain morphology and function in velo-cardio-facial syndrome (22q11.2 deletion syndrome). *American Journal of Medical Genetics part B: Neuropsychiatric Genetics, 141*, 274–280.

Kates, W. R., Miller, A. M., Abdulsabur, N., Antshel, K. M., Conchelos, J., Fremont, W., et al. (2006). Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *Journal of the American Academy of Child and Adolescent Psychiatry, 45*, 587–595.

Kesslak, J. P., Nagata, S. F., Lott, I., & Nalcioglu O. (1994). Magnetic resonance imaging analysis of age-related changes in the brains of individuals with Down's syndrome. *Neurology, 44*, 1039–1045.

Kippenhan, J. S., Olsen, R. K., Mervis, C. B., Morris, C. A., Kohn, P., Lindenberg, A. M., et al. (2005). Genetic contributions to human gyrification: Sulcal morphometry in Williams syndrome. *Journal of Neuroscience, 25*, 7840–7846.

Kipps, C. M., Duggins, A. J., Mahant, N., Gomes, L., Ashburner, J., & McCusker, E. A. (2005). Progression of structural neuropathology in preclinical Huntington's disease: A tensor based morphometry study. *Journal of Neurology Neurosurgery and Psychiatry, 76*, 650–655.

Krasuski, J. S., Alexander, G. E., Horwitz, B., Rapoport, S. I., & Schapiro, M. B. (2002). Relation of medial temporal lobe volumes to age and memory function in nondemented adults with Down's syndrome: Implications for the prodromal phase of Alzheimer's disease. *American Journal of Psychiatry, 159*, 74–81.

Kurotaki, N., Imaizumi, K., Harada, N., Masuno, M., Kondoh, T., Nagai, T., et al. (2002). Haploinsufficiency of NSD1 causes Sotos syndrome. *Nature Genetics, 30*, 365–366.

Lai, C. S., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F., & Monaco, A. P. (2001). A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature, 413*, 519–523.

Lai, C. S., Gerrelli, D., Monaco, A. P., Fisher, S. E., & Copp, A. J. (2003). FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. *Brain, 126*, 2455–2462.

Lemaitre, H., Crivello, F., Dufouil, C., Grassiot, B., Tzourio, C., Alperovitch, A., et al. (2005). No epsilon4 gene dose effect on hippocampal atrophy in a large MRI database of healthy elderly subjects. *Neuroimage, 24*, 1205–1213.

Levitin, D. J., Menon, V., Schmitt, J. E., Eliez, S., White, C. D., Glover, G. H., et al. (2003). Neural correlates of auditory perception in Williams syndrome: An fMRI study. *Neuroimage, 18*, 74–82.

Lieberman, J. A., Tollefson, G. D., Charles, C., Zipursky, R., Sharma, T., Kahn, R. S., et al. (2005). Antipsychotic drug effects on brain morphology in first-episode psychosis. *Archives of General Psychiatry, 62*, 361–370.

Lind, J., Larsson, A., Persson, J., Ingvar, M., Nilsson, L. G., Backman, L., et al. (2006). Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: relation to chronological age and recognition memory. *Neuroscience Letters, 396*, 23–27.

Lott, I. T., & Head E. (2001). Down syndrome and Alzheimer's disease: A link between development and aging. *Mental Retardation and Developmental Disabilities Research Reviews, 7*, 172–178.

Martin, N. G., Boomsma, D. I., & Machin, G. (1997). A twin-pronged attack on complex traits. *Nature Genetics, 17*, 387–392.

Mascalchi, M., Lolli, F., Della, N. R., Tessa, C., Petralli, R., Gavazzi, C., et al. (2004). Huntington disease: volumetric, diffusion-weighted, and magnetization transfer MR imaging of brain. *Radiology, 232*, 867–873.

Mekel-Bobrov, N., Gilbert, S. L., Evans, P. D., Vallender, E. J., Anderson, J. R., Hudson, R. R., et al. (2005). Ongoing adaptive evolution of ASPM, a brain size determinant in Homo sapiens. *Science, 309*, 1720–1722.

Meng, Y., Zhang, Y., Tregoubov, V., Janus, C., Cruz, L., Jackson, M., et al. (2002). Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. *Neuron, 35*, 121–133.

Meyer-Lindenberg, A., Kohn, P., Mervis, C. B., Kippenhan, J. S., Olsen, R. K., Morris, C. A., et al. (2004). Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. *Neuron, 43*, 623–631.

Meyer-Lindenberg, A., Buckholtz, J. W., Kolachana, B., Hariri, R., Pezawas, L., Blasi, G., et al. (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 6269–6274.

Morris, C. A., Mervis, C. B., Hobart, H. H., Gregg, R. G., Bertrand, J., Ensing, G. J., et al. (2003). GTF2I hemizygosity implicated in mental retardation in Williams syndrome: genotype-phenotype analysis of five families with deletions in the Williams syndrome region. *American Journal of Medical Genetics A, 123*, 45–59.

Murphy, K. C., Jones, L. A., & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry, 56*, 940–945.

Nemoto, K., Ohnishi, T., Mori, T., Moriguchi, Y., Hashimoto, R., Asada, T., et al. (2006). The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. *Neuroscience Letters, 397*, 25–29.

Nokelainen, P. & Flint, J. (2002). Genetic effects on human cognition: lessons from the study of mental retardation syndromes. *Journal of Neurology Neurosurgery and Psychiatry, 72*, 287–296.

Paulsen, J. S., Magnotta, V. A., Mikos, A. E., Paulson, H. L., Penziner, E., Andreasen, N. C., et al. (2006). Brain structure in preclinical Huntington's disease. *Biological Psychiatry, 59*, 57–63.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D. L., Blumenthal, J., Giedd, J. N., et al. (1999). Structural maturation of neural pathways in children and adolescents: in vivo study. *Science, 283*, 1908–1911.

Pearlson, G. D., Breiter, S. N., Aylward, E. H., Warren, A. C., Grygorcewicz, M., Frangou, S., et al. (1998). MRI brain changes in subjects with Down syndrome with and without dementia. *Developmental Medicine and Child Neurology, 40*, 326–334.

Peinemann, A., Schuller, S., Pohl, C., Jahn, T., Weindl, A., & Kassubek J. (2005). Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. *Journal of the Neurological Sciences, 239*, 11–19.

Pennington, B. F., Filipek, P. A., Lefly, D., Chhabildas, N., Kennedy, D. N., Simon, J. H., et al. (2000). A twin MRI study of size variations in human brain. *Journal of Cognitive Neuroscience, 12*, 223–232.

Peper, J. S., Zwiers, M. P., van Leeuwen, M., Van den Berg, S. M., Boomsma, D. I., Kahn, R. S., et al. (2004). Genetic modeling of cognitive brain maturation in pre-adolescence: A longitudinal study in twins. *Twin Research and Human Genetics, 7*, S172.

Pezawas, L., Verchinski, B. A., Mattay, V. S., Callicott, J. H., Kolachana, B. S., Straub, R. E., et al. (2004). The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *Journal of Neuroscience, 24*, 10099–10102.

Pfefferbaum, A., Sullivan, E. V., Swan, G. E., & Carmelli D. (2000). Brain structure in men remains highly heritable in the seventh and eighth decades of life. *Neurobiology of Aging, 21*, 63–74.

Pfefferbaum, A., Sullivan, E. V., & Carmelli D. (2004). Morphological changes in aging brain structures are differentially affected by time-linked environmental influences despite strong genetic stability. *Neurobiology of Aging, 25*, 175–183.

Pinter, J. D., Brown, W. E., Eliez, S., Schmitt, J. E., Capone, G. T., & Reiss, A. L. (2001). Amygdala and hippocampal volumes in children with Down syndrome: a high-resolution MRI study. *Neurology, 56*, 972–974.

Pinter, J. D., Eliez, S., Schmitt, J. E., Capone, G. T., & Reiss, A. L. (2001). Neuroanatomy of Down's syndrome: a high-resolution MRI study. *American Journal of Psychiatry, 158*, 1659–1665.

Posthuma, D. & Boomsma, D. I. (2000). A note on the statistical power in extended twin designs. *Behavioral Genetics, 30*, 147–158.

Posthuma, D., de Geus, E. J.C., Neale, M. C., Pol, H. E.H., Baare, W. E.C., Kahn, R. S., et al. (2000). Multivariate genetic analysis of brain structure in an extended twin design. *Behavior Genetics, 30*, 311–319.

Posthuma, D., de Geus, E. J., Baare, W. F., Hulshoff Pol, H. E., Kahn, R. S., & Boomsma, D. I. (2002). The association between brain volume and intelligence is of genetic origin. *Nature Neuroscience, 5*, 83–84.

Rakic, P., Bourgeois, J. P., & Goldman-Rakic, P. S. (1994). Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. *Progression in Brain Research, 102*, 227–243.

Raz, N., Torres, I. J., Briggs, S. D., Spencer, W. D., Thornton, A. E., Loken, W. J., et al. (1995). Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: evidence from MRI morphometry. *Neurology, 45*, 356–366.

Reiss, A. L., Eliez, S., Schmitt, J. E., Straus, E., Lai, Z., Jones, W., et al. (2000). IV. Neuroanatomy of Williams syndrome: a high-resolution MRI study. *Journal of Cognitive Neuroscience, 12*(Suppl 1), 65–73.

Reiss, A. L., Eckert, M. A., Rose, F. E., Karchemskiy, A., Kesler, S., Chang, M., et al. (2004). An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. *Journal of Neuroscience, 24*, 5009–5015.

Reveley, A. M., Reveley, M. A., Chitkara, B. & Clifford, C. (1984). The genetic basis of cerebral ventricular volume. *Psychiatry Research, 13*, 261–266.

Rosas, H. D., Goodman, J., Chen, Y. I., Jenkins, B. G., Kennedy, D. N., Makris, N., et al. (2001). Striatal volume loss in HD as measured by MRI and the influence of CAG repeat. *Neurology, 57*, 1025–1028.

Rosas, H. D., Koroshetz, W. J., Chen, Y. I., Skeuse, C., Vangel, M., Cudkowicz, M. E., et al. (2003). Evidence for more widespread cerebral pathology in early HD: An MRI-based morphometric analysis. *Neurology, 60*, 1615–1620.

Rosas, H. D., Hevelone, N. D., Zaleta, A. K., Greve, D. N., Salat, D. H., & Fischl B. (2005). Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. *Neurology, 65*, 745–747.

Santos, K. F., Mazzola, T. N., & Carvalho, H. F. (2005). The prima donna of epigenetics: The regulation of gene expression by DNA methylation. *Brazilian Journal of Medical and Biological Research, 38*, 1531–1541.

Scamvougeras, A., Kigar, D. L., Jones, D., Weinberger, D. R., & Witelson, S. F. (2003). Size of the human corpus callosum is genetically determined: an MRI study in mono and dizygotic twins. *Neuroscience Letters, 338*, 91–94.

Schmitt, J. E., Eliez, S., Warsofsky, I. S., Bellugi, U., & Reiss, A. L. (2001a). Enlarged cerebellar vermis in Williams syndrome. *Journal of Psychiatric Research, 35*, 225–229.

Schmitt, J. E., Eliez, S., Warsofsky, I. S., Bellugi, U., & Reiss, A. L. (2001b). Corpus callosum morphology of Williams syndrome: Relation to genetics and behavior. *Developmental Medicine and Child Neurology, 43*, 155–159.

Schmitt, J. E., Watts, K., Eliez, S., Bellugi, U., Galaburda, A. M., & Reiss, A. L. (2002). Increased gyrification in Williams syndrome: Evidence using 3D MRI methods. *Developmental Medicine and Child Neurology, 44*, 292–295.

Simon, T. J., Ding, L., Bish, J. P., McDonald-McGinn, D. M., Zackai, E. H., & Gee J. (2005). Volumetric, connective, and morphologic changes in the brains of children with chromosome 22q11.2 deletion syndrome: an integrative study. *Neuroimage, 25*, 169–180.

Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: A structural MRI study. *Developmental Medicine and Child Neurology, 44*, 4–16.

Sugama, S., Bingham, P. M., Wang, P. P., Moss, E. M., Kobayashi, H., & Eto Y. (2000). Morphometry of the head of the caudate nucleus in patients with velocardiofacial syndrome (del 22q11.2). *Acta Paediatrica, 89*, 546–549.

Sullivan, E. V., Pfefferbaum, A., Swan, G. E., & Carmelli D. (2001). Heritability of hippocampal size in elderly twin men: equivalent influence from genes and environment. *Hippocampus, 11*, 754–762.

Swillen, A., Devriendt, K., Legius, E., Prinzie, P., Vogels, A., Ghesquiere, P., et al. (1999). The behavioural phenotype in velocardio-facial syndrome (VCFS): From infancy to adolescence. *Genetic Counseling, 10*, 79–88.

Szeszko, P. R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., et al. (2005). Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Molecular Psychiatry, 10*, 631–636.

Teipel, S. J., Schapiro, M. B., Alexander, G. E., Krasuski, J. S., Horwitz, B., Hoehne, C., et al. (2003). Relation of corpus callosum and hippocampal size to age in nondemented adults with Down's syndrome. *American Journal of Psychiatry, 160*, 1870–1878.

Teipel, S. J., Alexander, G. E., Schapiro, M. B., Moller, H. J., Rapoport, S. I., & Hampel H. (2004). Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. *Brain, 127*, 811–824.

Thieben, M. J., Duggins, A. J., Good, C. D., Gomes, L., Mahant, N., Richards, F., et al. (2002). The distribution of structural neuropathology in pre-clinical Huntington's disease. *Brain, 125*, 1815–1828.

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., et al. (2001). Genetic influences on brain structure. *Nature Neuroscience, 4*, 1253–1258.

Thompson, P. M., Lee, A. D., Dutton, R. A., Geaga, J. A., Hayashi, K. M., Eckert, M. A., et al. (2005). Abnormal cortical complexity and thickness profiles mapped in Williams syndrome. *Journal of Neuroscience, 25*, 4146–4158.

Toga, A. W., & Thompson, P. M. (2004). Genetics of Brain Structure and Intelligence. *Annual Review of Neuroscience, 28*, 1–23.

Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping brain maturation. *Trends in Neurosciences, 29*, 148–159.

Tomaiuolo, F., Di Paola, M., Caravale, B., Vicari, S., Petrides, M., & Caltagirone C. (2002). Morphology and morphometry of the corpus callosum in Williams syndrome: A T1-weighted MRI study. *Neuroreport, 13*, 2281–2284.

van Amelsvoort, T., Daly, E., Henry, J., Robertson, D., Nguyen, V., Owen, M., et al. (2004). Brain anatomy in adults with velocardiofacial syndrome with and without schizophrenia: preliminary results of a structural magnetic resonance imaging study. *Archives of General Psychiatry, 61*, 1085–1096.

Vargha-Khadem, F., Watkins, K., Alcock, K., Fletcher, P., & Passingham, R. (1995). Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder.*Proceedings of the National Academy of Sciences of the United States of America, 92*, 930–933.

Vink, J. M., & Boomsma, D. I. (2002). Gene finding strategies. *Biological Psychology, 61*, 53–71.

Wang, P. P., Hesselink, J. R., Jernigan, T. L., Doherty, S., & Bellugi, U. (1992). Specific neurobehavioral profile of Williams' syndrome is associated with neocerebellar hemispheric preservation. *Neurology, 42*, 1999–2002.

Watkins, K. E., Vargha-Khadem, F., Ashburner, J., Passingham, R. E., Connelly, A., Friston, K. J., et al. (2002). MRI analysis of an inherited speech and language disorder: structural brain abnormalities. *Brain, 125*, 465–478.

Weickert, C. S., Hyde, T. M., Lipska, B. K., Herman, M. M., Weinberger, D. R., & Kleinman, J. E. (2003). Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Molecular Psychiatry, 8*, 592–610.

Weis, S., Weber, G., Neuhold, A., & Rett, A. (1991). Down syndrome: MR quantification of brain structures and comparison with normal control subjects. *AJNR American Journal of Neuroradiology, 12*, 1207–1211.

White, N. S., Alkire, M. T., & Haier, R. J. (2003). A voxel-based morphometric study of nondemented adults with Down Syndrome. *Neuroimage, 20*, 393–403.

White, T., Andreasen, N. C., & Nopoulos P. (2002). Brain volumes and surface morphology in monozygotic twins. *Cerebral Cortex, 12*, 486–493.

Woods, R. P., Freimer, N. B., De Young, J. A., Fears, S. C., Sicotte, N. L., Service, S. K., et al. (2006). Normal Variants of Microcephalin and ASPM Do Not Account for Brain Size Variability. *Human Molecular Genetics, 15*, 2025–2029.

Wright, I. C., Sham, P., Murray, R. M., Weinberger, D. R., & Bullmore, E. T. (2002). Genetic contributions to regional variability in human brain structure: methods and preliminary results. *Neuroimage, 17*, 256–271.