Purpose: Craniosynostosis (CRS) is a congenital condition resulting premature fusion of one or more cranial sutures. CRS is classified according to the involved sutures into sagittal, metopic, unicoronal, unilambdoid, bicoronal, and multiple-suture CRS, with sagittal suture fusion known to be the most common type. Although multiple studies have presented demographic characteristics of CRS patients, to date, there is no study representing an Asian population. We sought to compare the demographic characteristics of Asian patients to those of Western patients, considering previous reports.

Materials and methods: A total of 266 CRS patients treated in a single institution from 1996 to 2016 were retrospectively reviewed. Data from the patients was collected regardless of whether they underwent operation. Patients’ age at the time of presentation, sex, and maternal and paternal age at birth were reviewed. Patients were routinely investigated for abnormal genes (FGFR2 and FGFR3). The Bayley Scales of Infant Development, Second Edition (BSID-II), was used to assess the patients’ cognitive and psychomotor development. One-way analysis of variance or the Kruskal–Wallis test was used to compare continuous variables. A p value of <0.05 was considered statistically significant.

Results: Our study included 157 males (59.02%) and 109 females (40.98%), with an age ranging from 0.1 to 10.5 years. The mean age at the time of diagnosis was 2.01 ± 2.57 years, and the mean age at operation was 2.16 ± 2.61 years. Of the patients, 27 (10.15%) were bicoronal, 28 patients (10.53%) were metopic, 48 patients (18.04%) were unicoronal, 50 patients (18.80%) were unilamboid, and 67 patients (25.19%) were sagittal. Patients with multiple-suture CRS totaled 46 (17.29%). Investigation of abnormal genes revealed six patients (2.20%), including two patients with abnormal FGFR2 and four patients with abnormal FGFR3.

Maternal and paternal ages at the patients’ birth were 32.18 ± 4.56 years and 34.71 ± 4.72 years, respectively. The mean BSID-II scores were 84.96 ± 22.77 for the Mental Development Index and 84.19 ± 25.62 for the Psychomotor Development Index. To examine the trend of diagnosis of CRS type, we also evaluated the number of new patients diagnosed with nonsyndromic CRS per year at our institution. New diagnoses of CRS generally increased from the year 2009, although variations continued.

Conclusion: The mean age of our patients is relatively high compared to previous, Western studies. Through this research, we recognized that cultural discrepancies regarding the expectations of Asian parents may lead to prolonged diagnosis of CRS patients, and yet even relatively older CRS infants can successfully be treated with surgical intervention. The prevalence of CRS types and BSID-II development scores varied compared to those in previous Western studies. Further investigations at the genetic level are required to compare the different populations. To diagnose CRS in an effective and timely manner, a physician must be aware of the general characteristics and understand the variations between Western and Eastern populations.
(Kapp-Simon et al., 2007). CRS may present as an isolated condition or as part of a complex craniofacial syndrome. Although the precise pathogenesis of CRS remains unclear, studies have shown that CRS is intimately related to abnormalities of osteoprogenitor cells within the cranial sutures, due to gene mutations in fibroblast growth factor receptors (FGFR) and the Mx homeobox (Slater et al., 2008).

Craniosynostosis is further classified according to the involved sutures into sagittal, metopic, unicoronal, unilambdoid, bicoronal, and multiple-suture CRS, with sagittal suture fusion known to be the most common type (Ghali et al., 2002). The skull morphology is closely related to the pattern of suture closure; sagittal CRS results in scaphocephaly; unicoronal and unilambdoid CRS result in plagiocephaly; and bicoronal and bilambdoid CRS result in relatively symmetric yet brachycephalic head shapes.

Although multiple studies have presented demographic characteristics of CRS patients, to date, there is no study representing Korean or any other Asian population. Thus our work involved examining the demographic characteristics of Korean CRS patients as a selected sample of an Asian population, to provide general guidelines that will aid surgeons in diagnosing and managing Asian CRS patients. Also we sought to compare the demographic characteristics of Asian patients to those of Western patients based on previous reports.

2. Materials and methods

A total of 266 CRS patients treated at a single institute from 1996 to 2016 were retrospectively reviewed. Data from the patients was collected regardless of whether they underwent operation. Patients’ age at the time of presentation, sex, and maternal and paternal age at birth were reviewed. Patients with syndromic CRS as well as those with a history of previous CRS operation were excluded. Patients were routinely investigated for abnormal genes (FGFR2 and FGFR3) because these are the most commonly involved genetic mutations in CRS (Johnson and Wilkie, 2011).

The Bayley Scales of Infant Development, Second Edition (BSID-II), was used to assess the patients’ cognitive and psychomotor development, as this is a standardized, norm-referenced objective test of an infant’s developmental status (Bayley, 1993). The BSID-II provides updated norms, yielding a Mental Development Index (MDI) and Psychomotor Development Index (PDI). The BSID-II scores are often categorized as accelerated, >115; within normal limits, 85–115; mildly delayed, 70–84; or severely delayed, <70 (Bayley, 1993; Starr et al., 2007).

Means and standard deviations were calculated for all continuous variables, as appropriate. Categorical variables were expressed as proportions (%). One-way analysis of variance or the Kruskal–Wallis test was used to compare continuous variables. All statistical analyses were assessed with the Statistical Package for Social Sciences (SPSS version 23.0; SPSS Inc., Armonk, NY, USA). A p value of <0.05 was considered statistically significant.

3. Results

Between 1996 and 2016, a total 266 CRS patients were included; 157 males (59.02%) and 109 females (40.98%), with an age range of 0.1–10.5 years. The mean age at the time of diagnosis was 2.01 ± 2.57 years, while the mean age at operation was 2.16 ± 2.61 years. General patient characteristics are presented in Table 1. A total of 220 patients had single-suture CRS; the sagittal type was the most frequent, while the bicoronal was the least frequent. Twenty-seven patients (10.15%) were bicoronal, 28 patients (10.53%) were metopic, 48 patients (18.04%) were unicoronal, 50 patients (18.80%) were unilambdoid, and 67 patients (25.19%) were sagittal. There were 46 patients (17.29%) with multiple-suture CRS. The CRS type and sex distribution of each group is shown in Table 2 and Fig. 1. Interestingly, metopic type CRS showed a sex ratio of a much greater number of males in our study as well as previous studies (Speltz et al., 2007; Zakhray et al., 2014).

Investigation of abnormal genes revealed six patients (2.20%), two patients with abnormal FGFR2 and four patients with abnormal FGFR3. The two patients with abnormal FGFR2 were multiple types, and four patients with abnormal FGFR3 were metopic, sagittal, unicoronal, and multiple types.

Maternal and paternal ages at the patients’ birth were 32.18 ± 4.56 years and 34.71 ± 4.72 years, respectively. When maternal and paternal ages were analyzed for each group, the mean maternal and paternal ages were the highest for the sagittal type (33.05 ± 4.68 years and 35.59 ± 5.15 years, respectively), whereas the lowest means were noted in the multiple-suture type (30.72 ± 5.75 and 33.78 ± 6.18 years). Yet there was no statistically significant difference between the groups regarding maternal and paternal ages (p = 0.17 and 0.53, respectively). Parental ages by types are summarized in Table 3.

The mean BSID-II scores were 84.96 ± 22.77 for MDI and 84.19 ± 25.62 for PDI. The mean MDI scores ranged from 77.21 ± 26.73 for the metopic type to 90.45 ± 22.46 for the unilambdoid type, while the mean PDI scores ranged from 71.32 ± 30.65 for the metopic type to 86.21 ± 24.56 for the unilambdoid type. The lowest mean scores of both MDI and PDI were noted in the metopic type, and the highest mean scores were noted in the unilambdoid type (Table 4 and Fig. 2). As with parental ages, however, there was no significant difference between the CRS types associated with BSID-II (p = 0.36 for MDI and 0.33 for PDI).

To see the trend of diagnosis of CRS type, we also evaluated the number of new patients diagnosed with nonsyndromic CRS per year at our institution (Fig. 3 and Table 5). New diagnoses of CRS generally increased from year 2009, although variations continued.

4. Discussion

Despite CRS having been considered as a purely cosmetic problem for long time by parents as well as by surgeons, this concept had changed over the past few decades. The ultimate goal of treatment includes normal morphology as well as craniofacial development. Studies have shown multiple functional impairments in those patients, including visual impairment, increased intracranial tension, brain growth restriction, and neuropsychiatric disorders (Panchal et al., 2001; Magge et al., 2002; Bristol et al., 2004; Siatkowski et al., 2005; Kordestani et al., 2006). Neurocognitive
impairments such as verbal short-term memory and language are reported to be as high as 35%–50% in school-aged children with CRS (Kapp-Simon et al., 2007). Because the causal implications of this association are partly unclear, many surgeons recommend routine neurodevelopmental tests of CRS patients, to help to identify patients at high risk for neurodevelopmental delay; thus earlier intervention could be considered to alleviate future problems (Lekovic et al., 2004; Speltz et al., 2007). As a result, multidisciplinary care guidelines recommended early neurodevelopmental screening before the age of 4 months, which should be continued until the age of 8 years (McCarthy et al., 2012).

### Table 2
Patient distribution of craniosynostosis type (in comparison to previous studies).

<table>
<thead>
<tr>
<th>Type</th>
<th>Current study</th>
<th>Speltz et al.</th>
<th>Zakhary et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(age and sex)</td>
<td>(age and sex)</td>
<td>(age and sex)</td>
</tr>
<tr>
<td>Bicoronal</td>
<td>27 (10.15%; 8 male, 19 female)</td>
<td>27 (21.60%; 18 male, 9 female)</td>
<td>13 (13%; 8 male, 5 female)</td>
</tr>
<tr>
<td>Metopic</td>
<td>28 (10.53%; 24 male, 4 female)</td>
<td>28 (22.40%; 6 male, 22 female)</td>
<td>31 (31%; 23 male, 5 female)</td>
</tr>
<tr>
<td>Unicoronal</td>
<td>48 (18.04%; 19 male, 29 female)</td>
<td>8 (6.40%; 3 male, 5 female)</td>
<td>10 (10%; 5 male, 5 female)</td>
</tr>
<tr>
<td>Unilambdoid</td>
<td>50 (18.80%; 29 male, 21 female)</td>
<td></td>
<td>2 (2%; 1 male, 1 female)</td>
</tr>
<tr>
<td>Multiple</td>
<td>46 (17.29%; 31 male, 15 female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sagittal</td>
<td>67 (25.19%; 46 male, 21 female)</td>
<td>62 (49.60%; 49 male, 13 female)</td>
<td>44 (44%; 36 male, 8 female)</td>
</tr>
</tbody>
</table>

### Table 3
Maternal and paternal ages at patient birth by craniosynostosis type.

<table>
<thead>
<tr>
<th>Type</th>
<th>Maternal age (y)</th>
<th>Paternal age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicoronal</td>
<td>32.57 ± 4.29</td>
<td>33.78 ± 4.58</td>
</tr>
<tr>
<td>Metopic</td>
<td>32.87 ± 4.22</td>
<td>35.47 ± 5.01</td>
</tr>
<tr>
<td>Unicoronal</td>
<td>31.24 ± 4.21</td>
<td>34.54 ± 3.83</td>
</tr>
<tr>
<td>Unilambdoid</td>
<td>32.74 ± 3.66</td>
<td>34.82 ± 3.47</td>
</tr>
<tr>
<td>Multiple</td>
<td>30.72 ± 5.75</td>
<td>33.78 ± 6.18</td>
</tr>
<tr>
<td>Sagittal</td>
<td>33.05 ± 4.68</td>
<td>35.59 ± 5.15</td>
</tr>
<tr>
<td>p Value</td>
<td>0.17</td>
<td>0.53</td>
</tr>
</tbody>
</table>

### Table 4
Neurodevelopment scores by craniosynostosis type.

<table>
<thead>
<tr>
<th>Type</th>
<th>BSID-II MDI</th>
<th>BSID-II PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicoronal</td>
<td>89.30 ± 24.50</td>
<td>88.25 ± 26.43</td>
</tr>
<tr>
<td>Metopic</td>
<td>77.21 ± 26.73</td>
<td>71.32 ± 30.65</td>
</tr>
<tr>
<td>Unicoronal</td>
<td>85.87 ± 21.67</td>
<td>83.87 ± 23.59</td>
</tr>
<tr>
<td>Unilambdoid</td>
<td>90.45 ± 22.46</td>
<td>86.21 ± 24.56</td>
</tr>
<tr>
<td>Multiple</td>
<td>82.26 ± 20.06</td>
<td>85.30 ± 26.26</td>
</tr>
<tr>
<td>Sagittal</td>
<td>83.35 ± 22.58</td>
<td>85.59 ± 24.58</td>
</tr>
<tr>
<td>p Value</td>
<td>0.36</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Craniosynostosis is a condition that is relatively commonly encountered by plastic and reconstructive surgeons, and in which the role of surgical treatment is of great importance. The recent concepts in CRS correction are focused on correction of the morphological deformity while minimizing neuropsychological dysfunctions (Lekovic et al., 2004). Skull deformity and probable increased intracranial pressure are often considered as potential causes of neurodevelopmental impairment. Surgical intervention varies from the traditional cranial remodeling to the relatively recently proposed distraction osteogenesis, which has gained popularity worldwide since its introduction by Sugawara et al. in 1998 (Sugawara et al., 1998; Forrest and Hopper, 2013). Since rapid brain volume expansion proceeds until the age of 3 years, and since...
about 90% of the adult size is reached by the age of 6 years, early surgical intervention is critical (Shim et al., 2016). Yet, CRS is an unfamiliar topic in many other fields of medicine, and a physician must understand patient characteristics for timely diagnosis and intervention. Thus we analyzed Asian CRS patients to provide general information and to compare characteristics with those of Western patients.

In previous studies, Speltz et al. reported CRS patients with mean age of 6.5 ± 3.9 months at diagnosis, and Zakhary et al. presented mean age of 8.9 months (range 5–30 months) at operation (Speltz et al., 2007; Zakhary et al., 2014). However, these studies excluded patients above 3 and 2 years old, respectively. In our study, the mean age at diagnosis was 2.01 ± 2.57 years. This is quite high compared to the previously mentioned studies, but we did not exclude any older patients because we wanted to show the actual raw ages of visiting CRS patients. Even if the visiting plagiocephalic infant is older than 2 or 3 years, a physician must not rule out the possibility of CRS. Parents who visited our department with relatively old CRS patients often stated that their elder family members recommended waiting, hoping for recovery of the cranial shape as the infant grew older. Although the raw age data for CRS patients at diagnosis and operation in previous Western studies are not available, some cultural discrepancies may have affected the delay in CRS diagnosis. Despite variations nowadays, many Asians emphasize family discipline and try to follow their elders’ teaching and recommendation. Interestingly, the new births in Korea have gradually decreased since 2000, but CRS diagnoses have generally increased, especially from 2010 (Fig. 1 and Table 5) (KOSIS, 2017). We believe that thorough screening examinations as well as improved knowledge of parents and physicians has led to increased diagnosis, which also included relatively old CRS patients as mentioned above.

There are some similar and different traits of the CRS type distribution among previous studies and ours. Traditionally, sagittal type is known to be the most common type, and our study supports this, showing 25.19% of the patients with this type (Ghali et al., 2002). Studies vary, with the second most common type varying between unicoronal and metopic CRS (Bennett et al., 2016). Speltz et al. presented patients of whom 49.60% were sagittal, 21.60% were metopic, 22.40% were unicoronal, and 6.4% were lambdoid (Speltz et al., 2007). Zakhary reported patients of whom 44.00% were sagittal, 31.00% metopic, 13.00% bicoronal, 10.00% unicoronal, and 2.00% multiple-suture CRS (Zakhary et al., 2014). In our study, the most to least common types were sagittal (25.19%), unicoronal (18.80%), unicoronal (18.04%), multiple-suture (17.29%), metopic (10.53%), and bicoronal CRS (10.15%), respectively (Table 2 and Fig. 1). Further studies are needed involving larger population, but our findings show that the epidemiology of CRS types may differ between Western and Eastern populations.

Variations were noted on neurodevelopment indices as well. Starr et al. presented mean MDI score of 92.08 and PDI score 84.85 for patients under 30 months, and Speltz et al. gave a mean MDI score of 91.92 ± 9.19 and PDI score of 84.00 ± 12.03 for infants and young children under 24 months (Speltz et al., 2007; Starr et al., 2007). Both studies show MDI scores greater than PDI scores, with mild psychomotor development delay. In our study, the mean scores were MDI 84.96 ± 22.77 and PDI 84.19 ± 25.62, showing lower MDI scores and similar PDI scores compared to other studies. Such a discrepancy may be due to the wider range of ages of CRS patients in our study. Both mean scores were within normal limits, and physicians must consider the wide variation of neurodevelopment in CRS patients. As mentioned earlier, the brain volume rapidly expands at younger ages, so a doctor must thoroughly discuss the risk and benefits of cranioplasty with patients with relatively older CRS children. As with parental ages, there was no significant difference between the CRS types associated with BSID-II. Yet metopic CRS patients showed relatively low mean scores compared to other types, and taking such trend as a reference, a physician may expect relatively low MDI and PDI scores when treating a metopic CRS patient.

Since 2010, the availability of whole exome and genome approaches greatly accelerated genetic research of genes enriched for mutations in CRS patients (Twig and Wilkie, 2015). Recent studies advocate a stronger influence of genetic factors in the etiopathogenesis of nonsyndromic CRS. One study proposed that targeted FGFR1, FGFR2, FGFR3, and TWIST1 genetic testing is appropriate as a first-line test for CRS patients, and that analyses of TCF12 and ERF are justified in all patients with coronal synostosis who are negative for FGFR and TWIST1 mutations (Lattanzi et al., 2017). Another study stated that at least 57 genetic mutations are associated with CRS, but realistically only a few of these are included in routine laboratory genetic testing (Miller et al., 2017). In our study, 6 patients (2.26%) were reported with abnormal FGFR genes. No specific gene anomaly seemed to be associated with a CRS type, but a much greater number of patients is required for a genetic conclusion. Further investigations at the genetic level are required to compare different populations. Despite extreme genetic heterogeneity of nonsyndromic CRS, genetic analysis may aid in early diagnosis of clinically ambiguous cases. Although nonsurgical treatment of CRS remains unavailable so far, advances in genetic research may open a new era in the future.

### 5. Conclusion

Through our experience, we support that young to even relatively older CRS infants and young children can successfully be treated with surgical intervention. To diagnose CRS in an effective and timely manner, a physician must be aware of the general characteristics and understand the variations between Western and Eastern populations. Our data showed relatively late diagnosis of CRS in an Asian population, possibly due to cultural background and misinformation. Furthermore, a thorough education of the population is required, targeted to parents as well as physicians. As mentioned earlier, CRS is not only a morphological disorder but also is closely associated with neurodevelopmental impairment. Only through appropriate, timely diagnosis can a CRS patient be treated with better outcomes and minimal complications.

### Ethical approval

This study was conducted in accordance with the Declaration of Helsinki.
Conflicts of interest
The authors declare that they have no conflict of interest.

References
KOSIS: Korean statistical information service. kosis.kr; 2017