X-linked Malformation Deafness: Neurodevelopmental Symptoms Are Common in Children With IP3 Malformation and Mutation in POU3F4

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INTRODUCTION

Congenital hearing loss occurs in one to three of 1000 newborns. At least 50% of these are of genetic causes where more than 100 loci have so far been cataloged for nonsyndromic deafness (Van Camp & Smith 2019). Affected genes include transcription factors, ion channels, and structural proteins. Of this, 1% to 5% (1/50,000 births) of all human hereditary hearing loss is thought to be X-linked (Petersen et al. 2008). Six nonsyndromic loci have been mapped to the X-chromosome (DFNX1-6) (Petersen et al. 2008; Corvino et al. 2018), where other loci on the X-chromosome have been shown to be syndromic (Tranebjærg et al. 1995). Five genes have been identified as being causative within these loci: PRPS1, POU3F4, SMPX, AIFM1, and COL4A6 (Corvino et al. 2018). DFNX2 is the most common of these (around 50% of cases) and is caused by a variety of mutations within the POU3F4 gene or its regulatory elements (Petersen et al. 2008; Corvino et al. 2018).

On imaging of the temporal bone, children with mutations in this gene display a typical malformation of the inner ear (Gong et al. 2014), classified as incomplete partition type 3 (IP3) (Sennaroglu et al. 2006). The cochleae demonstrate aplasia of the modiolus and osseous spiral lamina but with the lateral interscalar septa present and a wide fundus with absence of the cribriform plate. Lacking this bony partition, the cochlea communicates directly with a widened internal auditory canal.

The function of POU3F4 is not fully understood. It encodes a POU-domain transcription factor, expressed in fibrocytes within the otic capsule and is involved in mesenchymal–mesenchymal cell signaling during labyrinthine development in association with another gene, TBX1 (Braunstein et al. 2008). POU3F4, along with the gene EPHA4, is also important in spiral ganglion fasciculation in the spiral ligament and essential for correct ganglion innervation (Coate et al. 2012). It is also expressed in the developing brain and kidney (Petersen et al. 2008; Cosse-Etchepare et al. 2018) although functional studies within these organs are lacking. Mutations within POU3F4 lead to a severe mixed or sensorineural hearing loss, which in most patients affect all audiometric frequencies and can be progressive (Petersen et al. 2008).
Children with hearing impairment develop cognitive abilities and language with other tools than children with typical hearing, and do not always have the same access to auditory stimuli and linguistic information (Walker et al. 2015). If a child does not have sufficient access to audible speech, a period of auditory deprivation occurs (Glick & Sharma 2017), which has a negative long-term effect on the development of listening skills, language, and more general cognitive processing skills (Lyxell et al. 2009; Kronenberger et al. 2013; Kral et al. 2016; Kronenberger et al. 2020). The deaf infant’s brain will eventually start to reorganize during these periods of auditory deprivation, and functions that are designed for listening may instead be wired to visual processing (cortical cross-modal plasticity) (Glick & Sharma 2017). Children with hearing impairment may also have specific difficulties with incidental learning due to their poorer ability to perceive speech, and especially to overhear speech in noisy environments (Cole & Flexer 2020).

From studies in groups of typical hearing children with less able executive functions (EFs), for example, children with attention deficit hyperactivity disorder (ADHD), it is known that they have difficulties to inhibit unwanted behavior or verbal responses, to update cognitive processing with new information, and to shift between channels of information, and that these characteristic deficits are correlated to other cognitive and linguistic skills (Barkley 1997; Willcutt et al. 2005). Poor executive functioning may affect their performance in more cognitive composite activities such as reading, writing, communication, and math (Loe & Feldman 2007; Greven et al. 2014). Children with a CI have previously been shown to have atypical or delayed EF skills, including attention span and inhibition (Kronenberger et al. 2013; Löfkvist et al. 2020). Deficits in phonological working memory, which is related to cognitive processing and storing of linguistic units, has been found in many previous studies of CI users (Willstedt-Svensson et al. 2004; Figueras et al. 2008; Lyxell et al. 2009; Kronenberger et al. 2013; Löfkvist et al. 2020). There is a bidirectional relation between EF skills and lexical–semantic abilities, meaning that for instance better language knowledge may influence EF skills positively (Baddeley 2012). Kronenberger et al. (2020) investigated the development of language and EF in 41 children with CI compared to controls with typical hearing (n = 40). The authors found that EF skills predicted a large portion of language development in children with CI, while language delays did not fully explain group differences in EF development.

When assessing lexical–semantic abilities in various groups of school-aged children, we have previously found that those with CI had expressive vocabulary results that were similar to controls with typical hearing when controlling for age and nonverbal cognitive ability (Löfkvist et al. 2014). However, children with CI had statistically significant better results than children with typical hearing and autism spectrum disorder (ASD) and children with developmental language disorder (DLD) (Löfkvist et al. 2014). We have also shown that children with CI with typical nonverbal cognitive ability can achieve age-equivalent results on expressive vocabulary and semantic word fluency on a group level, while they may have poorer results on phonemically based word fluency (Löfkvist et al. 2012).

Furthermore, mental illness may be associated with children with profound hearing loss (Huber & Kipman 2011). However, children with CI have also been reported to have a mental ill-health status that is comparable to typical hearing peers (Anmyr et al. 2012). Better language ability may be related to a more positive health-related quality of life in children with CI (Haukedal et al. 2018).

We have previously reported on our surgical procedure and the hearing outcomes of cochlear implantation in 10 children with IP3 malformation (Smeds et al. 2017). That study revealed a group of children with more complex needs than other children with CIs in our clinic. Previous studies of cochlear implantation in this group have focused primarily on the surgical procedure, postoperative aspects, radiology, or genetic analysis and give limited information on linguistic, cognitive, and mental ill-health outcomes (Sennaroglu et al. 2006; Incesulu et al. 2008; Aschendorff et al. 2009; Lee et al. 2009; Stankovic et al. 2010; Kang et al. 2013; Busi et al. 2015; Cosetti et al. 2015; Choi et al. 2016; Kim et al. 2016; Saeed et al. 2016; Wester et al. 2016; Kim et al. 2018; Sennaroglu & Bajin 2018; Albballaa et al. 2019). The reported hearing and language outcomes vary from quite poor to results in line with pediatric CI recipients without inner ear malformation. Tian et al. (2018) recently reported hearing outcomes in 14 patients with IP3 malformation and compared them to a control group with normal cochlea anatomy. Auditory thresholds were similar between groups; however, those with cochlear malformation exhibited poorer consonant recognition after 1 year. Albballaa et al. (2019) have also reported good outcomes after implantation at both 1 and 3 years, in line with those with normal cochlea anatomy; however, programming strategies were difficult. Some of the studies have, without specific data, indicated that the children with X-linked deafness seem to have special needs and “attention disorders.”

Children with X-linked deafness have so far been classified as nonsyndromic. One would then expect that children in this subgroup who wear CI(s) have the same chance to develop similar linguistic outcomes as other children with CI(s) who have a typical nonverbal cognitive ability and no other related behavioral abnormalities (ASD or DLD). However, we and others suggest that poor spoken language could be related to poor speech recognition and low attention level (Lee et al. 2009; Stankovic et al. 2010; Smeds et al. 2017).

In the current study, we aimed to evaluate the hearing and cognitive functioning in a group of children with radiologically diagnosed IP3 cochlea malformation, where the surgical aspects of this group have already been reported (Smeds et al. 2017). These children were compared with a group of pediatric CI recipients with mutations in the GJB2 gene, a genetic cause of deafness that is not syndromic and not usually associated with neurodevelopmental disorders. We characterized the POU3F4 mutations in children with IP3 malformation and aimed to explore whether this subgroup had specific difficulties compared to controls in hearing and listening ability, spoken language, cognition, and mental ill-health. In particular, we were interested whether possible difficulties arose in these children that could not be related to their level of hearing alone.

**MATERIALS AND METHODS**

**Study Design**

A prospective cross-sectional study was designed to assess hearing outcomes, language, and mental ill-health in individuals with radiologically diagnosed IP3 cochlea malformation. All participants were invited to participate in a prospective
complementary assessment day, in combination with a retrospective chart review.

Five assessment areas were covered in the prospective part of the study: genetic analysis, hearing, spoken language, cognition, and mental ill-health (see Table 1). In addition, the family history of hearing loss and possible neurodevelopmental disorders were discussed with caregivers, as well as additional deficits of the child, linguistic background, educational level of parents and the current communication mode used by the child and family.

During the assessment day, the children met with several experienced professionals: a psychologist, a speech-language pathologist (SLP), a social worker, an audiologist, and a surgeon. A randomized test schedule was used and the psychologist was blinded for type of etiology in all the participating children. The test administrators only used spoken language while performing the tests. However, initial test instructions were accompanied with supported signs if needed, which was the case for some children with IP3 malformation. None of the children in the control group needed sign-supported instructions.

Participants
During the years 2007 to 2015, nine boys and one girl with severe-profound mixed hearing loss were identified with radiological findings consistent with IP3 cochlear malformation (Sennaroglu et al. 2006) within Sweden and subsequently referred to the national center for children with malformed cochlea; Hearing Implant Clinic (HIC), Karolinska University Hospital in Stockholm. Fifteen cochlear implantations were performed (five sequential bilateral) and patients were then seen on regular follow-up visits at the HIC (cases X01–X10, Table 2). All 10 families agreed to participate in this study. The results from cases X01 to X10 were compared with a control group (n = 10) of pediatric CI recipients without cochlear malformation. This control group was matched in age, sex, parent’s education level, and nonverbal cognitive ability, and chosen to be homogeneous for a mutation in Connexin 26 (GJB2 gene), although not for a single specific mutation within the gene. The control group is presented as cases C01–C10 in Table 2. Parents of 13 children with mutations in GJB2 agreed to participate, where the older children were also asked to sign a letter of consent. Two children with mutations in GJB2 were excluded as they were hearing aids only and one family asked to terminate the study, due to their own choice. Three girls and seven boys comprised the control group. All families (N = 20) participated in the assessment day.

Measures
Genetic Analysis • Genetic screening by a team of clinical and laboratory geneticists was performed in all children with IP3 malformation (n = 10) for the POU3F4 gene. If a mutation was previously detected, the mutation was confirmed with the methods used in this study. Multiplex ligation probe amplification (MLPA) was carried out according to standard protocols in order to detect deletions and duplications in the POU3F4 gene as well as in a conserved region 1Mb upstream of the gene (P163-D1, MRC-Holland, GJB-WSF1-POU3F4 probe mix). An analysis of selected point mutations in GJB2, GJB3, GJB6, and WFS1 were included in the kit. If a mutation was not detected with MLPA, POU3F4 was sequenced through traditional Sanger sequencing protocols. Primer sequences and laboratory conditions are available upon request.

Hearing and Listening Ability
Aided sound field hearing thresholds were assessed in children older than 4 years, by presenting frequency-modulated tones at octave frequencies from 0.125 to 8 kHz. Testing was performed using both the left and the right CI individually for children with bilateral CIs. Speech recognition in quiet, in multisource noise, and sound localization was tested using previously described methods (Asp et al. 2011, 2012). In brief, speech recognition in quiet was measured with a 25-item list of monosyllabic words, presented at 65 dB SPL. The speech signal was presented directly in front of the child under both quiet and noisy conditions, with the latter condition including the presentation of stationary speech-shaped uncorrelated noise from ±45° and ±135° azimuth, resulting in a signal-to-noise ratio of 0 dB. Sound localization was measured in the frontal horizontal plane by presenting pink noise pulse trains at 65 dB SPL (randomly roved ±5 dB) from five equally spaced loudspeakers between −90° and 90° azimuth. A test consisted of 10

| TABLE 1. The abilities and analyses measured in the study where assessment tools are shown in italics |
|-----------------------------------------------|
| Genetic Analysis | Hearing and Listening Ability | Spoken Language Abilities | Cognition | Mental ill-Health |
| MLPA | Aided sound field thresholds | Expressive vocabulary (BNT) | Nonverbal cognitive ability (Raven) | Parent and teacher questionnaire (SDQ) |
| Sanger sequencing | Speech in quiet | Analysis of Lexical-semantic error types (BNT) | Executive functioning: test of everyday attention for children (TEA-Ch) |
| | Sound localization | Semantic word fluency AND Phonemic word fluency (Animal fluency and FAS letter fluency) | Executive functioning: parent and teacher questionnaire (BRIEF) |
| | | Expressive grammar level (Löfkvist et al. 2014) | Phonological working memory (Serial recall of nonwords; Wass, Reference Note 6) |
| | | Pragmatic skills; parent questionnaire (CCC-2) | General working memory (Sentence Completion and Recall task; Wass 2009) |
| | | Speech intelligibility rating (SIR-2, Allen et al. 2001) | General cognitive ability (Bayley-III) |
| | | | Emotional Behavioral and Attention Rating Scale (Löfkvist et al. 2020) |

BNT, Boston Naming Test; CCC-2, Children’s Communication Checklist-2; SDQ, Strengths and Difficulties Questionnaire.
| Child | Sex | Age of ID | First Visit | 1st Age | 2nd Age | HL 1st | HL 2nd | Bimodal | Follow-up | 1st Age | Education | Father Education | Communication | Mode Postimplant | School Setting | Additional Conditions | Family Relations |
|-------|-----|-----------|------------|---------|---------|--------|--------|---------|-----------|---------|----------|-----------------|---------------|----------------|---------------|-----------------------|------------------|
| X01   | M   | 0; 2      | 1; 1       | 1; 6    | 2; 3    | Bilat  | CI     | Yes, HA | 9; 8      | 1; 1    | 1        | Spoken language | Mainstream school | Under investigation for ADHD | Brother to X03 |
| X02   | M   | 1; 8      | 2; 0       | 2; 2    |         |        |        |        | 9; 9      | 2; 1    | 1        | Spoken language | Mainstream school |                         |               |
| X03   | M   | 0; 2      | 0; 7       | 1; 0    | 2; 0    | Bilat  | CI     | Yes, HA | 7; 4      | 2; 1    | 1        | Spoken language | Mainstream school | Mild motor delay | ADHD, Asperger's | Brother to X01 |
| X04   | M   | 0; 2      | 0; 7       | 0; 9    |         |        |        |        | 7; 2      | 1; 2    | 2        | Bilingual (spoken and sign) | Special unit | ADHD | Second cousin to X04/X06 |
| X05   | M   | 0; 2      | 0; 7       | 1; 6    | 2; 7    | Bilat  | CI     | Yes, HA | 7; 2      | 2; 1    | 2        | Bilingual (spoken and sign) | Special unit | ADHD |                      |
| X06   | M   | 0; 3      | 0; 6       | 1; 0    | 2; 5    | Bilat  | CI     | Yes, HA | 5; 6      | 1; 2    | 2        | Bilingual (spoken and sign) | Deaf preschool | Mainstream preschool |ADHD | Brother to X04 |
| X07   | F   | 0; 2      | 1; 8       | 2; 3    |         |        |        |        | 4; 2      | 2; 1    | 2        | Spoken language with supportive signs (Swedish and Arabic) | Mainstream preschool with special assistant | ADHD | Severe motor delay | Parents are cousins |
| X08   | M   | 0; 3      | 2; 6       | 2; 8    | 3; 8    | Bilat  | CI     |         | 0; 1      | 1; 1    | 2        | Spoken language with supportive signs | Mainstream preschool | ADHD, Mild motor delay |                |
| X09   | M   | 0; 2      | 1; 1       | 1; 7    |         |        |        |        | 3 weeks   | 2; 2    | 2        | Bilingual (spoken and sign) | Mainstream preschool | Autism spectrum disorder |                |
| X10   | M   | 0; 2      | 2; 6       | 2; 7    |         |        |        |        | 2; 8      | 2; 2    | 2        | Spoken language with supportive signs | Mainstream preschool |                |                |
| Mean  |     | 0; 4      | 1; 4       | 1; 8    | 2; 7    |        |        |        | 6; 0      | 1; 6    | 1.7      |                |               |                |                |                      |
| Median|     | 0; 2      | 1; 1       | 1; 7    | 2; 5    |        |        |        | 6; 4      | 2; 0    | 2.0      |                |               |                |                |                      |
| C01   | F   | 2; 0      | 5; 1†      | 5; 5    |         |        |        |        | 14; 7     | 2; 2    | 2        | Spoken language and signs (Swedish and polish) | Special unit |                |                |                      |
| C02   | M   | 0; 2      | 0; 5       | 0; 8    | 0; 8    | Bilat  | CI     |         | 9; 1      | 1; 1    | 1        | Bilingual (spoken and sign) | Mainstream preschool |                |                |                      |
| C03   | M   | 0; 2      | 0; 3       | 0; 7    |         |        |        |        | 1; 10     | 1; 1    | 1        | Spoken language | Mainstream preschool |                |                |                      |
| C04   | M   | 0; 7      | 3; 8       | 4; 0    |         |        |        |        | 5; 8      | 1; 1    | 1        | Spoken language | Mainstream school |                |                |                      |
| C05   | M   | 0; 2      | 0; 3       | 0; 6    |         |        |        |        | 1; 6      | 1; 1    | 1        | Spoken language | Mainstream school | Mild balance disorder |                |                      |
| C06   | M   | 0; 2      | 0; 7       | 0; 9    | 0; 9    | Bilat  | CI     |         | 3; 8      | 2; 2    | 2        | Spoken language | Mainstream preschool |                |                |                      |
| C07   | M   | 0; 7      | 1; 5       | 1; 6    | 1; 9    | Bilat  | CI     |         | 12; 7     | 1; 1    | 1        | Bilingual (spoken and sign) | Mainstream school |                |                |                      |
| C08   | M   | 0; 2      | 0; 7       | 0; 8    | 0; 8    | Bilat  | CI     |         | 4; 5      | 1; 2    | 2        | Spoken language with assistant | Mainstream preschool |                |                |                      |
| C09   | F   | 0; 2      | 0; 9       | 1; 1    |         |        |        |        | 5; 1      | 2; 2    | 2        | Bilingual (spoken and sign) | Mainstream preschool |                |                |                      |
| C10   | F   | 0; 1      | 2; 2       | 2; 9    |         |        |        |        | 7; 6      | 2; 2    | 2        | Bilingual (spoken and sign) | Mainstream preschool | Asthma |                | Sister to C10 |
| Mean  |     | 0; 5      | 1; 6       | 1; 9    | 1; 1    |        |        |        | 6; 6      | 1.4    | 1.8      |                |               |                |                |                      |
| Median |     | 0; 2      | 1; 3       | 0; 6    | 0; 9    |        |        |        | 5; 5      | 1.0    | 2.0      |                |               |                |                |                      |

**Table 2.** Participant demographics and hearing history on individual and group level (IP3 malformation and GJB2)

- Age and follow-up is expressed as (years; months).
- Mother/Father education level: 1 = University, 2 = High school.
- No neonatal screening in country of origin.
- Family immigrated when the child was five.
- Sequential bilateral cochlear implantation pending.
- ADHD, attention deficit hyperactivity disorder; CIC, Hearing Implant Clinic; F, female; HA, hearing aid; IP3, incomplete partition type 3; L, left; M, male; R, right.
presentations (two stimuli per loudspeaker). Presentation order was randomized and children either verbally indicated the perceived sounding loudspeaker (which was labeled) or by pointing at it. Sound localization was quantified by an Error Index (Gardner & Gardner 1973; Asp & Reinfeldt 2018) ranging from 0 (perfect performance) to 1 (random performance).

**Spoken Language Abilities** • Expressive vocabulary and naming ability were examined with the 60-item Boston Naming Test (BNT) in all children older than 4 years (Kaplan et al., Reference Note 3). Children were asked to name the pictures orally, and had the same standardized instructions (Tallberg 2005). Raw scores from BNT were transferred to stanine and compared to Swedish norms for children with typical hearing (Tallberg 2005).

**Word Fluency Ability** • Two different word fluency tasks were conducted in children older than 4 years. First, FAS letter fluency is performed where children are instructed verbally to generate as many words as possible within one minute beginning with the letter F, then A and then S. This phonemically based word fluency task has been validated and normed in a Swedish cohort of 130 typically developed children between 6 and 15 years (Tallberg et al. 2011) and assesses both linguistic competence like lexical organization and executive functioning in individuals (Löfkvist et al. 2014). Second, animal fluency task, where children are asked to name as many animals within 1 minute, which measures word retrieval skills and lexical-semantic knowledge. The instructions were initially given orally in the same way for all children, and then the child had to confirm that he/she had understood before the test started.

The test-administer made audio recordings, with the purpose to confirm that he/she had understood before the test started.

**The Speech Intelligibility Rating Scale-2 (SIR-2)** was used in this study to rate the level of understandable speech in all children at the time of follow-up (Allen et al. 2001). This rating scale was originally developed for use in children with hearing impairment with CI, and consists of a five-level rating scale that is rated by an SLP at a certain test occasion. The SIR scale was originally validated in 54 English children (1; 2–10 years) (Allen et al. 2001). SIR is implemented at the HIC, but has so far not been validated in a Swedish context.

Expressive grammar scale ranging from level 1: “no use of voice with intent” to level 8 “typical or correct expressive grammar and sentence level” was rated for all children at the test occasion by the same SLP (Löfkvist et al. 2014; Smeds et al. 2017). This rates the expressive and syntactic level of children with CI from certain test occasions. It is rated from the child’s spontaneous speech production in verbal interaction and play situations with the SLP and the child’s caregivers. Although in clinical use at the HIC, it has also been used in research (Löfkvist, Reference Note 4).

**Pragmatic Skills** • A parent-report questionnaire evaluating pragmatic skills in everyday communication; Children’s Communication Checklist-2 (CCC-2) was included for children older than 4 years and analyzed with computerized scoring (Bishop, Reference Note 2). The CCC-2 comprises of 70 different statements in the questionnaire that was filled out by the participant’s caregivers. The questionnaire consists of 10 subscales; A (speech), B (syntax), C (semantics), D (coherence), E (inappropriate initiations), F (stereotypic language), G (use of context), H (nonverbal communication), I (social relations), and J (interests). One can also generate a total score: General Communication Composite. The CCC-2 has previously been normalized in a Swedish context for children 4 to 16 years (https://www.pearsonassessment.se/ccc-2).

**Cognition** • Nonverbal cognitive ability was tested in children older than 4 years with the Ravens colored progressive matrices test (Raven et al., Reference Note 5). This test evaluates an individual’s ability to discover and interpret visual patterns and can be considered a screening tool for intelligence quotient (IQ).

EFs were examined in older children by a blinded psychologist and an SLP. The psychologist used the Test of Everyday Attention for Children (TEA-Ch) to assess EF in children older than 6 years of age (Manly et al. 2001). The TEA-Ch consists of nine subtests, each focusing on a specific aspect of EF (Sky Search, Score!, Creature Count, Sky Search DT, Map Mission, Walk – Don’t Walk, Opposite Worlds and Code Transmission.) Each subtest is given in either an auditory or visual modality. We excluded the subtest Score Dual Task, as it was too difficult for the children with CI to discriminate between the two sound tracks in the test, thus making the measure unreliable. Furthermore, all sessions with the psychologist were videotaped with the purpose to observe and rate the children’s emotional, behavioral and attention abilities during the testing situation by using an in-house Emotional Behavioral and Attention Rating (EBA-R) scale (see Appendix 1 in Supplemental Digital Content 1, http://links.lww.com/EANDH/A836). The test administrator observed and rated the children during the testing and this was validated with the help of the video material later. Bayley Scales of infant and Toddler development (Bayley-III) was used to evaluate developmental quotient and cognitive functioning in children younger than five years (Bayley, Reference Note 1). Two children (X04 and C04) who were older (5; 6 and 5; 9, respectively) were also evaluated with Bayley-III, because they were not able to participate in the TEA-Ch test.

**Phonological and General Memory Ability** • Serial recall of nonwords (Wass, Reference Note 6) was used to assess phonological working memory, and a relatively pure measure of the phonological loop capacity (Baddeley 2003). Children older than 5 years listened to standardized recorded nonword material presented from loudspeakers, with gradually increasing numbers of nonwords in a row, and they were asked to repeat the nonword utterances as accurately as they could. The percent of correctly reproduced words was calculated. General working memory (i.e., the capacity to simultaneously store and process information) was assessed by means of the Sentence Completion and Recall task (Wass, Reference Note 6). This material was also presented to children older than 5 years, with live voice. These two working memory tasks have been used in both children with typical hearing and in clinical groups, including children with hearing impairment (Lyxell et al. 2009; Henricson et al. 2012). The data material was recorded for later analysis of the child’s utterances. A qualitative analysis of semantic relevant or irrelevant types of responses on the general working memory task was conducted by the test administrator (SLP), who used a method that previously had been used for the evaluation of possible semantic relevance in error lexical responses on an expressive vocabulary test (Löfkvist et al. 2014). In addition, Behavior Rating Inventory of EF (BRIEF) questionnaires (BRIEF-P for younger children and BRIEF for older children) were used for the evaluation of ecologically based EFs in the children’s everyday environment (Gioia et al. 2000; Isquith et al. 2004). BRIEF functional scales are standardized parent-
teacher-reported questionnaires for screening of possible behavioral problems in executive functioning in different daily situations. BRIEF comprise eight subscales which are comprised in three different indexes; the Behavioral Regulation Index (BRI) with three subscales; Inhibit, Shift, Emotional control; the Metacognition Index including five subscales; Initiate, Working memory, Plan/Organize, Organization of Material, and Monitor. The third index is the global executive composite, which covers all eight subscales. The BRIEF questionnaires were filled out by caregivers of all children over 2 years of age, and teachers if the children were at preschool or school age.

Mental Health • Mental ill-health was assessed with Strengths and Difficulties Questionnaire (SDQ), which is developed for parents and teachers of children aged 2 to 4 years and 4 to 17 years (Goodman 1997, 2005). The SDQ is a 25-item screening questionnaire in which the items are grouped into five subscales containing five items each. The subscales are emotional symptoms, conduct problems, hyperactivity-inattention, peer problems, and prosocial behavior (Goodman 1997, 2005). A total difficulty score was calculated by adding the sum of scores on the emotional, conduct problems, hyperactivity-inattention, and peer problems subscales, with a possible range of 0 to 40 (Goodman 2005). The cutoff values are based on English normative SDQ scoring and thus set to 14 (Goodman 1997, 2005). The SDQ has been translated into Swedish and established as a valid and useful instrument with satisfactory reliability (Smedje et al. 1999; Malmberg et al. 2003). It also has been found to be a reliable and valid questionnaire for use in samples of children that are deaf or hard of hearing (Hintermair 2007; Anmýr et al. 2012).

In the current study, we used the version of the Swedish SDQ that includes an impact supplement with a three-band categorization. This investigated whether the rater (caregivers or teacher) was worried for the child’s mental health, and in which settings this was seen (home, school, and leisure activities) (Goodman 1999). The impact scores were categorized in to three categories by the test-administer. If parents and teachers reported that they were not worried at all, or “only a little,” the results were rated as zero raw score, while “a medium amount” was rated with a score of one and “a great deal” with a score greater than 1. Then, the total raw scores of completed SDQ from mothers, fathers, and teachers were categorized in the original three-band categorization (Goodman 1999). If the respondent (caregiver or teacher) had reported that the child exhibited “a medium amount” (one score) of behavior difficulty that led to a significant distress impairment in at least one domain setting that may impact on either the child’s home life, peer relations, classroom learning, or leisure time and it was classified a borderline. If the raters (caregivers of different sexes and/or teachers) had rated the children’s impact results between 2 and 10 raw scores, they were categorized as if the child had a great deal of distress impairment, which could indicate an abnormal situation and a possible psychiatric disorder (Goodman 1999).

Ethical Approval and Considerations

The study was approved by the Regional Review Board of Stockholm (2014/2068-31/2). All caregivers and children who were old enough to read initially received written information about the study and then agreed to participate and signed a letter of consent.

Statistical Analysis

Descriptive statistics and between-group comparisons of postoperative hearing thresholds, speech recognition, sound localization, language, and cognitive outcome were produced using Statistica version 13 (Statsoft) and SPSS, version 23. Due to the small size of the cohort, group comparisons were made by using nonparametric data analyses (Mann–Whitney U-tests, including effect size indicators; r = Z/√N, and Chi-square test to investigate possible differences in gender representation in the two groups).

RESULTS

On the day of multidisciplinary assessment, one child in the control group was sick and therefore only the parent-report questionnaires were included for this participant (C09), where the hearing test results were collected from the most recent medical records at the clinic. Case C03 was unable to participate in formal hearing and cognitive tests due to age (2; 0), and in combination with fatigue at the day of data collection.

In the experimental group (patients X01–X10), four children used total communication (sign language and spoken Swedish, Table 2). The majority of children in both groups primarily used spoken language and attended mainstream preschools and schools, with or without individual support in the classrooms. One child in each group had parents who spoke another spoken language at home. Four children (proband 3 and 5) with IP3 malformation had been diagnosed with ADHD, where one had a concurrent diagnosis of Asperger’s syndrome. Another participant is currently under investigation for ADHD (proband 1). A sixth child with IP3 malformation deafness has been diagnosed with ASD (Table 2). None of the caregivers in the experimental group reported hereditary factors for ADHD. None of the caregivers in the control group reported a family history of neurodevelopmental disorders and there were no children in the control group with concurrent diagnoses at the time of the study.

The formal test results are presented within the five areas of investigation: genetics, hearing and listening ability, spoken language, cognition, and mental ill-health. Results are presented at group and individual levels and with group comparisons of children with IP3 malformation and children with mutations in GJB2 mutations. There was no statistical difference between the groups (IP3 versus GJB2 mutations) regarding age, sex, or parents educational level neither for mothers or fathers (ps > 0.05).

Genetic Analysis

Known mutations in POU3F4 were detected in five of the children with MLPA analysis and with Sanger sequencing. Previously undescribed point mutations were found in an additional two children, which resulted in a frameshift located in the POU domain. Including previously performed genetic testing, mutations affecting POU3F4 were detected in nine out of 10 patients, eight males and one female (Fig. 1 and Table 3), representing six probands. In two families, two brothers were affected. In addition, in one of these families a second cousin (male) was affected. All affected boys with familial IP3 malformation shared the same mutation.

Case X07 was the first child to parents who are cousins. She presented with hearing loss and low muscle tone. Array-CGH revealed a de novo 8.21 Mb heterozygous interstitial deletion
Children with IP3 malformation had statistically significantly lower scores than controls on the phonological working memory task (Serial recall of nonsense word-2) \( (Z = -2.08, p = 0.01, r = 0.72) \) but not on total scores on the general working memory task (Sentence Completion and Recall) (Table 5). However, a systematic and qualitative analysis of error responses on the Sentence Completion and Recall task revealed a group-specific difference with more semantic irrelevant responses in the group of children with IP3 malformation than in children with \textit{GJB2} mutations \( (Z = -2.68, p = 0.01, r = 0.72) \). For example, the response of a child with IP3 malformation when the test
administer says: “In the sea swims…” could be “boats” where the target word was fish, ducks or similar.

**Emotional Behavioral Attention: Rating During the Psychological Test Situation**

Children older than 6 were assessed by EBA-R. Here, children with IP3 malformation showed statistically significantly higher levels in three out of six parameters with (1) more frustration ($Z = -2.12, p = 0.03, r = 0.50$); (2) more restlessness ($Z = -2.50, p = 0.01, r = 0.69$); and (3) a less structured ability in different problem solving tasks regarding logical behavior ($Z = -2.39, p = 0.02, r = 0.63$), and close to significant regarding a lesser degree of focus ($p > 0.05$) compared to controls (Fig. 6). There were no statistical differences between groups (IP3 malformation versus GJB2 mutation) regarding expression of positive emotions during the test situation or degree of unstructured behavior in problem solving (expression of chaotic behavior).

**Mental Health**

A comparison between the surveys performed by parents of children in the IP3 malformation group and control group, and between teachers in the same two groups, showed some significant differences. Parents of children in the IP3 malformation group reported significantly higher scores on total difficulties ($Z = -2.37, p = 0.02, r = 0.37$), hyperactivity-inattention ($Z = -2.59, p = 0.01, r = 0.45$), conduct problems ($Z = -2.11, p = 0.04, r = 0.30$), and impact score ($-3.44, p < 0.01, r = 0.79$) than controls with GJB2, and significantly lower scores on prosocial behavior ($Z = 2.18, p = 0.03, r = 0.32$) (Fig. 7). There were no statistically significant differences on two subscales: emotional symptoms and peer problems ($p > 0.05$).

Teachers of children in the IP3 malformation group reported significantly higher scores on peer problems ($Z = -2.40, p = 0.02, r = 0.48$), hyperactivity-inattention ($Z = -2.24, p = 0.03, r = 0.45$), and impact score ($Z = 2.12, p = 0.03, r = 0.37$, and

**TABLE 3. Genetic findings in participants with IP3 malformation (n = 10)**

| Case Identifier | Proband | Year of Birth | Sex | MLPA | Sanger Sequencing | Previously Performed Genetic Testing | Carrier Status of the Mother |
|-----------------|---------|---------------|-----|------|-------------------|--------------------------------------|-----------------------------|
| X01*            | 1       | 2005          | M   | NP   | NP                | Hemizygous deletion in POU3F4 (PCR)  | Obligate carrier            |
| X02             | 2       | 2005          | M   | Mutation not detected | Mutation not detected | 100 kb deletion upstream (PCR)       | NP                          |
| X03*            | 1       | 2008          | M   | Mutation not detected | Mutation not detected | 500 kb deletion upstream (PCR)       | NP                          |
| X04†            | 3       | 2008          | M   | Mutation not detected | Mutation not detected | Heterozygous deletion of 4 probes upstream (PCR) | NP                          |
| X05‡            | 3       | 2008          | M   | Mutation not detected | Mutation not detected | Heterozygous deletion of 4 probes upstream (PCR) | NP                          |
| X06†            | 3       | 2009          | M   | Mutation not detected | Mutation not detected | Hemizygous deletion upstream (422-427kb) | Obligate carrier            |
| X07             | 4       | 2011          | F   | Mutation not detected | Mutation not detected | Heterozygous deletion of 2 probes in exon 1 | Array CGH normal            |
| X08             | 5       | 2013          | M   | Mutation not detected | Mutation not detected | 704del (POU domain)                  | C.666-866del                 |
| X09             | 6       | 2013          | M   | Mutation not detected | Mutation not detected | Heterozygous deletion of 2 probes in exon 1 | Phe235Serfs*6 (POU domain)  |
| X10             | 7       | 2012          | M   | Mutation not detected | Mutation not detected | Hemizygous deletion of 6 probes upstream (PCR) | Array CGH normal            |

*Patients 1 and 3 are brothers (proband 1).
† Patients 4 and 6 are brothers (proband 3).
‡ Patient 5 is a second cousin to patients 4 and 6 (proband 3).
F, female; M, male; MLPA, multiplex ligation probe amplification; NP, not performed.

Fig. 2. Hearing Thresholds with CI. Aided frequency-modulated tone threshold measured in sound field. Left and right ears are pooled (IP3 malformation: n = 14 ears; GJB2: n = 18 ears). Mean and standard error are indicated.
they reported significantly lower scores on prosocial behavior for children with IP3 malformation ($Z = -2.24, p = 0.03, r = 0.42$) (Fig. 7). There were no statistically significant differences on three subscales: total difficulties, emotional symptoms, and conduct problems ($p > 0.05$).

All mothers and almost all fathers of the IP3 malformation group rated the children in a way that indicated mental ill-health on total difficulties. Moreover, parents reported mental ill-health with hyperactivity-inattention (restlessness, difficulty concentrating, and a lack of ability to think things out before

### TABLE 4. Hearing, listening, and spoken language outcome for all participants (N = 20)

| Case Identifier (years; months) | Speech in Quiet (%) | Speech in Noise (%) | Sound Localization | Expressive Grammar In-House Scale (0–8) | Speech Intelligibility, SIR-2 (0–5) | Expressive Vocabulary BNT (Raw Scores/Stanine) | Word Fluency |
|---------------------------------|--------------------|---------------------|-------------------|-----------------------------------------|--------------------------------------|-----------------------------------------------|-------------|
| X01 (9;6)                       | 64                 | 44                  | 0.19              | 8                                       | 5                                    | 32/2                                           | 21          |
| X02 (9;3)                       | 48                 | 20                  | 0.50              | 7                                       | 4                                    | 23/1                                           | 16          |
| X03 (6;9)                       | 48                 | 8                   | 0.56              | 7                                       | 3                                    | 14/1                                           | 7           |
| X04 (6;8)                       | 52                 | 20                  | 0.38              | 7                                       | 3                                    | 6/*                                            | 12          |
| X05 (6;9)                       | 8                  | *                   | 0.38              | 7                                       | 3                                    | *                                              | 8           |
| X06 (4;9)                       | 52                 | 20                  | 0.19              | 7                                       | 3                                    | 21/1                                           | *           |
| X07 (3;6)†                      | 4                  |                     |                   |                                         |                                      |                                                |             |
| X08 (3;6)†                      | 3                  |                     |                   |                                         |                                      |                                                |             |
| X09 (2;0)†                      | 2                  |                     |                   |                                         |                                      |                                                |             |
| X10 (2;9)†                      | 2                  |                     |                   |                                         |                                      |                                                |             |
| Mean                            | 45                 | 24                  | 0.36              | 6                                       | 3                                    | 19/1                                           | 14          |
| SD                              | 19.2               | 13.1                | 0.15              | 2.2                                     | 1.2                                  | 10.7/0.4                                       | 5.9         |
| Median                          | 50                 | 20                  | 0.38              | 6                                       | 3                                    | 21/1                                           | 14          |
| C01 (14;5)                      | 84                 | *                   | 0.38              | 8                                       | 5                                    | 31/1                                           | 18          |
| C02 (8;9)                       | 96                 | 56                  | 0.00              | 8                                       | 5                                    | 49/9                                           | 20          |
| C03 (2;0)†                      | 4                  |                     |                   |                                         |                                      |                                                |             |
| C04 (5;8)                       | 64                 | 56                  | 0.88              | 7                                       | 5                                    | 23/4                                           | 1           |
| C05 (3;5)†                      | 7                  |                     |                   |                                         |                                      |                                                |             |
| C06 (1;6)†                      | 6                  |                     |                   |                                         |                                      |                                                |             |
| C07 (12;3)                      | 100                | 68                  | 0.06              | 8                                       | 5                                    | 52/9                                           | 37          |
| C08 (4;8)                       | 64                 | 32                  | 1.06              | 7                                       | 5                                    | 24/4                                           | *           |
| C09 (5;3)                       | 88                 | *                   | 0.44              | 8                                       | 5                                    | *                                              | *           |
| C10 (7;9)                       | 48                 | *                   | 0.38              | 8                                       | 5                                    | 34/4                                           | *           |
| Mean                            | 78                 | 53                  | 0.46              | 7                                       | 5                                    | 36/5                                           | 16          |
| SD                              | 19.3               | 15.1                | 0.39              | 1.3                                     | 0.9                                  | 12.4/3.2                                       | 14.0        |
| Median                          | 84                 | 56                  | 0.40              | 8                                       | 5                                    | 33/5                                           | 18          |

* Not done because of fatigue or unclear reasons.
† Not performed because of younger age.
acting). In the control group one mother and one father, each indicated mental ill-health for one child each, but not for the same child.

Children with IP3 malformation were more likely to have parents or teachers that rated their behavior as having a borderline or significant impact on their everyday life. This indicates that the parents were worried about the child’s mental condition, and a possible indication of psychiatric deficit (Table 6).

**DISCUSSION**

In this explorative study, we have been able to demonstrate that children with IP3 malformation deafness exhibit specific difficulties, not only in the domains of hearing but also in spoken language, and in some subdomains of cognition and mental health, compared with a control group with another nonsyndromic genetic cause of deafness (GJB2). This is an important consideration when clinicians discuss expected outcomes of cochlear implantation. Parents of these children would need to be informed that hearing outcomes are poorer compared to other groups with CI, and that neurodevelopmental symptoms are more common. A more in-depth assessment procedure and rehabilitation program should be considered.

**Genetics**

Nine of 10 of the participating children exhibited mutations in POU3F4 or its regulatory elements. Several of these patients were related where only six probands were identified. Related probands may have co-inherited traits that explain the related difficulties.

As a mutation in POU3F4 was not found in one participant (X02), despite displaying the IP3 phenotype, the temporal bone malformation might be related to mutations in other regulatory regions or other related genes. This could include mutations in TBX1 (Braunstein et al. 2008) or EPHA4 (Coate et al. 2012); however, these additional studies were not performed.

There have only been three reported studies of cochlear implantation in females with IP3 malformation deafness, including the female in our own report (Smeds et al. 2017), where two did not discuss genetic testing of those who participated in their study (Incesulu et al. 2008; Tian et al. 2018). Previously, Marlin et al. (2009) reported on eight females with POU3F4 anomalies, where cochlear implantation was not performed. Only three of them had hearing loss and only one of them had the radiography findings consistent with IP3. Our female patient (X07) had a large deletion on the X-chromosome, including POU3F4 and 19 other RefSeq genes. Sequencing of POU3F4 did not reveal an additional mutation on the other allele. The IP3 phenotype could possibly be explained by a skewed X-inactivation. The deletion detected was large and so a contiguous deletion syndrome could also occur, affecting other genes involved in intellectual disabilities. A more detailed analysis of this patient would be appropriate in the future, including X-inactivation studies or next generation mate pair deletion characterization. However, additional DNA studies have not been performed due to a limited DNA sample provided by the patient.

**Hearing and Listening Outcome**

Recent work has shown that speech perception of children with IP3 malformation is in line with those with normal cochlear anatomy at 1 and 3 years (Alballaa et al. 2019); however, programming strategies were difficult. While others have reported poorer outcomes and hypothesized that this outcome is due to poor consonant recognition, where vowel recognition is good (Tian et al. 2018). We have previously reported similar results (Smeds et al. 2017), and expanded this in the current study, where children with IP3 malformation exhibited worse speech recognition despite aided hearing thresholds comparable to those of children with a normal cochlea.

The difference in speech recognition existed in both quiet and noise, suggesting a poorer sound processing ability in the IP3 malformation group. This may be linked to limited spectral and/or temporal resolution related to intracochlear issues,
such as an abnormal spiral ganglion neuron organization due to its interaction with EPHA4 (Coate et al. 2012), but may also be related to inferior nerve signal transmission capacity or an altered ability of central sound processing. A similar poor speech recognition has been found in auditory neuropathy spectrum disorder (Teagle et al. 2010), where the defect lies central to a normal functioning cochlea. Whether the fault lies within the cochlea, nerve, or central processing pathways in this group is unclear and would be an important future direction. Alballaa et al. (2019) have reported that they could not obtain electrically evoked compound action potentials in patients with IP3 malformation in several electrodes suggesting that the fault may lie in the cochlea or its respective nerve.

Atypical Spoken Language and Cognitive outcome

The older children with IP3 malformation (X01–X06) exhibited specific difficulties in expressive vocabulary and semantic knowledge, speech intelligibility, cognitive processing skills, and speech recognition in noise, despite a typical nonverbal cognitive ability, and no other known hereditary causes for a familial language disorder or ADHD. Structured observation ratings of both older and younger children (C01, C02, C04, C07, C08, C10, and X01–X06) by the blinded psychologist, revealed an atypical behavior and characteristics of poorer emotional control and attention span, in children with IP3 malformation when compared to controls with GJB2 mutations, who behaved more in accordance with age. Parent and teacher reports revealed that children with IP3 malformation exhibited poorer executive functioning and pragmatics in home and school settings as well as poorer mental ill-health results when compared to controls. Considering that all children with POU3F4 related deafness demonstrated similar difficulties within all assessed domains (hearing, spoken language, cognition, and mental ill-health), we suggest that children with POU3F4-related deafness may exhibit a neurological component that is independent of their reduced hearing preoperatively.

It has been shown in several previous studies (Lee et al. 2009; Stankovic et al. 2010; Tian et al. 2018) that these children exhibit an improved hearing postoperatively. Despite this, their understanding and use of spoken language is poorer when compared to controls. The children with IP3 malformation performed poorly in the areas of expressive vocabulary, semantics, and pragmatics. However, it should be noted that this expressive language and speech intelligibility was improved when compared to preoperatively (Smeds et al. 2017). These findings suggest that spoken language is improved with cochlear implantation but not to a comparable level seen in control groups. The majority of the children with IP3 malformation attended mainstream schools showing that their verbal communication skills are at a satisfactory level, even if their lexical-semantic knowledge is poor. Nevertheless, it is yet unknown how their learning ability and social skills manifest in different listening environments, compared to typical hearing peers or matched controls with mutations in GJB2.

The umbrella term EF includes inter-related cognitive functions enabling purposeful, goal-directed behavior (Anderson 2002; Chan et al. 2008; Gathercole et al. 2008). Although the frontal lobes have been shown to be highly involved in executive functioning skills (Anderson 2002), these functions are the result of a network of activities involving almost every part of the brain (Heaton et al. 2001). Hence, many different kinds of disturbances of brain functioning can give rise to changes or disruptions in executive functioning skills, such as a reduced ability to persevere on monotonous tasks or increased vulnerability for disturbances. This could also be applied to IP3 malformation deafness. POU3F4 has been shown to be expressed in the brain (Petersen et al. 2008; Cosse-Etchepare et al. 2018); however, to the authors’ knowledge, functional studies have not been done. POU3F4 knock-out mice (Brn4−/−) show ultrastructure alterations in the cochlear but phenotypically do not exhibit gross brain abnormalities (Minowa et al. 1999), although specific studies to assess behavior in these animals have not been done. One could hypothesize that a nonfunctioning POU3F4 protein could lead to the attention deficit-type disorder that is seen in these children, especially as others have noted this behavioral pattern (Stankovic et al. 2010; Giannantonio et al. 2020), but functional studies are lacking to support this. In our study, we used the TEA-Ch test to target the children’s ability to sustain attention, to switch attention between tasks and to inhibit automatic responses (Heaton et al. 2001; Anderson 2002). The participating children commonly had difficulties with dual tasking in the EF assessment. The testing procedure was tiring for many children in both groups (IP3 malformation and mutations in GJB2), but more of the children with IP3 malformation either refused to perform a subtest or ran out of time and hence could not perform all tests.

The test administrator used an in-house created rating scale (EBA-R) for the evaluation and rating of the children’s
individual emotional, behavioral, and attentional performance during the assessment session, which has been used in a previous study of children with congenital cytomegalovirus (CMV) infection (Löfkvist et al. 2020). The children with IP3 deafness displayed significantly more restless behavior than controls, in a setting where the psychologist was blinded to the diagnoses of the participants.

It is possible that the children’s poor EF led to the exhibited poor attention. Furthermore, phonological working memory which is part of the EF domain was significantly poorer
for children with IP3 malformation than controls. This skill has previously been found to be difficult for children with CI, irrespective of their cause of deafness, and it has also been linked to language development (Casserly & Pisoni 2013). Therefore, children with IP3 malformation deafness might be at a greater disadvantage in lexical-semantic learning than other children with CI, independent of their poorer speech recognition in quiet and noise, which would influence incidental learning in everyday life (Cole & Flexer 2020). Finally, the parent and teacher BRIEF reports further strengthen the results from the more formal EF assessments, by showing that children with IP3 malformation had more EF difficulties in everyday settings like home, preschool, and school compared to controls.

Mental Ill-Health Outcome in Relation to Neurodevelopmental Disorders and Diagnoses

Analysis of SDQ data showed that children with IP3 malformation also exhibited mental health concerns related to emotional symptoms, conduct, hyperactivity-inattention, and prosocial behavior. This is in itself insufficient to diagnose a mental health disorder; however, four of the children in the IP3 malformation group have confirmed ADHD diagnoses, assessed by the standard clinical pathway for neurodevelopmental disorders at the pediatric departments in their home communities. We can also see, as the younger ones grow older, that questions of ADHD features arise in these children, where one is under investigation. Low IQ was only present in two children, in one together with additional psychomotor disability. One of the youngest children with POU3F4 related deafness has recently been diagnosed with ASD. None of the children in the control group had ADHD or signs of other neurodevelopmental disorders. X-chromosome mutation/deletion can be related to ADHD (Green et al. 2015). The sexual dimorphism that is present in ADHD suggests a role for the X-chromosome, where this is thought to include the number of X-chromosomes (e.g., Turner’s syndrome) or X-linked gene haploinsufficiency (Davies 2014). This is particularly important when one considers the large deletion found in X07, where other genes involved in behavior may have been affected. The other individuals in the current study may have escaped mutation in the genes associated with attention and behavior, such as MAOA (Biederman et al. 2008), HTR2C (Xu et al. 2009), and STS (Kent et al. 2008), but this was not explicitly examined in this study.

Comorbid Clinical Picture in Children With IP3 Malformation Deafness

It is well known that hearing impairment may be related to different levels of attention deficits in children (Beer et al. 2014; Kronenberger et al. 2014; Kral et al. 2016). One factor is the influence of auditory deprivation that can influence negatively on cognitive abilities like EF (Beer et al. 2014; Kronenberger et al. 2014). Our participants with IP3 malformation did not on average have a longer period of auditory deprivation before their first cochlear implantation (1.8 years) compared to controls (1.9 years). Other important factors that may influence positively on spoken language development in children with hearing impairment is their nonverbal cognitive ability (Moog & Geers 2003; Löfkvist, Reference Note 4) and higher education level of parents (Szagun & Stumper 2012). There were no significant differences in nonverbal cognitive ability or parental education level between groups.

Nonsyndromic causes of deafness from mutations on the X chromosome do not exhibit multiple comorbid conditions (Petersen et al. 2008) and are not known to have a higher risk
The study had similar raw scores on the general working memory task than controls, which indicates an additional diagnosis (Haukedal et al. 2020). However, when one looks at the interdisciplinary outcome data together, both the magnitude and the specific features of the comorbid symptom picture of children with IP3 malformation cannot be explained by poor speech perception alone, and this could indicate that additional phenotypes may be present that are part of a wider syndrome.

**Clinical Implications**

The clinical findings in this study, including neurodevelopmental symptoms and diagnoses in addition to hearing and
spoken language deficits, highlight the need for long-term and sustained follow-up of all children with IP3 malformation/X-linked hearing loss. With this new knowledge, counseling of the parents on the specific needs of these children and family support should be initiated at the earliest stage possible. Their low speech recognition, in combination with the special features of these children, indicate that altered training may be necessary, perhaps by combining auditory-verbal strategies with audiovisual, and in some situations more visual support. As soon as signs of cognitive disability present, pediatric psychiatry should be consulted to assess the extent of these disorders. The family should also be offered genetic counseling. Depending on the characteristics of the individual child it may be necessary to lower the expectations of the outcome with CI, but with special attention to training and support, the majority can develop oral communication and may attend mainstream schools with individual support.

CONCLUSION

Children with POUSF4 related IP3 malformation deafness exhibit features different from other children with cochlear implants. They exhibit poorer outcomes in hearing and spoken language while displaying a pattern of concentration difficulties, poor impulse control and hyperactivity, in formal tests, caregiver questionnaires and blinded observation of emotional, behavioral, and attention performance during testing. The neurodevelopmental symptoms were partly obvious, such as hyperactivity and below average development of hearing and language, but also subtler, such as poor phonological working memory, poor perseveration, and shallow language progress. A previous subgroup of nonsyndromic X-linked hearing loss, DFN1, was reclassified as Mohr-Tranebjærg syndrome as additional features were identified relating to the specific mutation on the X-chromosome (Tranebjærg et al. 1995). Our study of children with severe IP3 malformation suggests a connection to anomalies in the attention/hyperactivity/language and autism spectrum of disability. We suspect that POUSF4 mutation related deafness can be reclassified as a syndromic deafness with progressive mixed severe-profound hearing loss in coexistence with neurodevelopmental symptoms and diagnoses; however, more detailed genetic analysis and larger group sizes would be essential to make this transition.

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