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

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Objective: Incomplete partition type 3 (IP3) malformation deafness is a rare hereditary cause of congenital or rapid progressive hearing loss. The children present with a severe to profound mixed hearing loss and temporal bone imaging show a typical inner ear malformation classified as IP3. Cochlear implantation is one option of hearing restoration in severe cases. Little is known about other specific difficulties these children might exhibit, for instance possible neurodevelopmental symptoms.

Material and methods: Ten 2; 0 to 9; 6-year-old children with IP3 malformation deafness (nine boys and one girl) with cochlear implants were evaluated with a retrospective chart review in combination with an additional extensive multidisciplinary assessment day. Hearing, language, cognition, and mental ill-health were compared with a control group of ten 1; 6 to 14; 5-year-old children with cochlear implants (seven boys and three girls) with another genetic cause of deafness, mutations in the *GJB2* gene.

Results: Mutations in *POU3F4* were found in nine of the 10 children with IP3 malformation. Children with IP3 malformation deafness had an atypical outcome with low level of speech recognition (especially in noise), executive functioning deficits, delayed or impaired speech as well as atypical lexical-semantic and pragmatic abilities, and exhibited mental ill-health issues. Parents of children with IP3 malformation were more likely to report that they were worried about their child's psychosocial wellbeing. Controls, however, had more age-typical results in all these domains. Eight of 10 children in the experimental group had high nonverbal cognitive ability despite their broad range of neurodevelopmental symptoms.

Conclusions: While cochlear implantation is a feasible alternative for children with IP3 malformation deafness, co-occurring neurodevelopmental anomalies, such as attention deficit hyperactivity or developmental language disorder, and mental ill-health issues require an extensive and consistent multidisciplinary team approach during childhood to support their overall habilitation.

Key words: ADHD, Cochlear implantation, Developmental language disorder, Incomplete partition type 3, Mental health, POU3F4, Syndrome, X-linked malformation deafness.

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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).

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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; Sennaroğlu & Bajin 2018; Alballaa 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. Alballaa et al. (2019) have also reported good outcomes after implantation at both 1 and 3 years, in line with those with normal cochlear 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 wore 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 1 Mb 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.

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

Child	Sex	Age at ID of HL	Age First Visit at HIC	Age 1st CI	Age 2nd CI	Bimodal Stimulation?	Follow-Up Since 1st CI	Mother Education	Father Education	Communication Mode Postimplant	School Setting	Additional Conditions Diagnosed or Under nvestigation	Family Relationships
X01	M	0; 2	1; 1	1; 6	2; 3	Bilat CI	9; 8	1	1	Spoken language	Mainstream school	Under investigation for ADHD	Brother to X03
X02	M	1; 8	2; 0	2; 2		Yes, HA other ear	9; 9	2	1	Spoken language	Mainstream school		
X03	M	0; 2	0; 7	1; 0	2; 0	Bilat CI	7; 4	2	1	Spoken language	Mainstream school	Mild motor delay	Brother to X01
X04	M	0; 2	0; 7	0; 9		Yes, HA other ear	7; 2	1	2	Bilingual (spoken and sign)	Special unit	ADHD, Asperger's	Brother to X06
X05	M	0; 2	0; 7	1; 6	2; 7	Bilat CI	7; 2	2	2	Bilingual (spoken and sign)	Special unit	ADHD	Second cousin to X04/X06
X06	M	0; 3	0; 6	1; 0	2; 5	Bilat CI	5; 6	1	2	Bilingual (spoken and sign)	Deaf preschool	ADHD	Brother to X04
X07	F	0; 2	1; 8	2; 3		Yes, HA other ear	4; 2	2	2	Spoken language with supportive signs (Swedish and Arabic)	Mainstream pre-school, special assistant	Severe motor delay	Parents are cousins
X08	M	0; 3	2; 6	2; 8	3; 8	Bilat CI	0; 1	1	2	Spoken language with supportive signs	Mainstream preschool	ADHD, Mild motor delay	
X09	M	0; 2	1; 1	1; 7		Yes, HA other ear	3 weeks	2	2	Bilingual (spoken and sign)	Mainstream preschool	Autism spectrum disorder	
X10	M	0; 2	2; 6	2; 7		Yes, HA other ear	2; 8	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		Yes, HA other ear	14; 7	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	Bilingual (spoken and sign)	Mainstream preschool		
C03	M	0; 2	0; 3	0; 7		‡	1; 10	1	1	Spoken language	Mainstream preschool		Brother to C04
C04	M	0; 7	3; 8	4; 0		Yes, HA other ear	5; 8	1	1	Spoken language	Mainstream school		Brother to C03
C05	M	0; 2	0; 3	0; 6		‡	1; 6	1	1	Spoken language	Mainstream school with assistant	Mild balance disorder	
C06	M	0; 2	0; 7	0; 9	0; 9	Bilat CI	3; 8	2	2	Spoken language	Mainstream preschool		
C07	M	0; 7	1; 5	1; 6	1; 9	Bilat CI	12; 7	1	1	Bilingual (spoken and sign)	Mainstream school		
C08	M	0; 2	0; 7	0; 8	0; 8	Bilat CI	4; 5	1	2	Spoken language	Mainstream preschool with assistant		
C09	F	0; 2	0; 9	1; 1		Yes, HA other ear	5; 1	2	2	Bilingual (spoken and sign)	Mainstream preschool		Sister to C10
C10	F	0; 1	2; 2	2; 9		Yes, HA other ear	7; 6	2	2	Bilingual (spoken and sign)	Mainstream preschool	Asthma	Sister to C09
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				

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 of confirming own notes (the child's responses) during the testing.

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 administer (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- and

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; Anmyr 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; $r = Z/\sqrt{N}$, 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

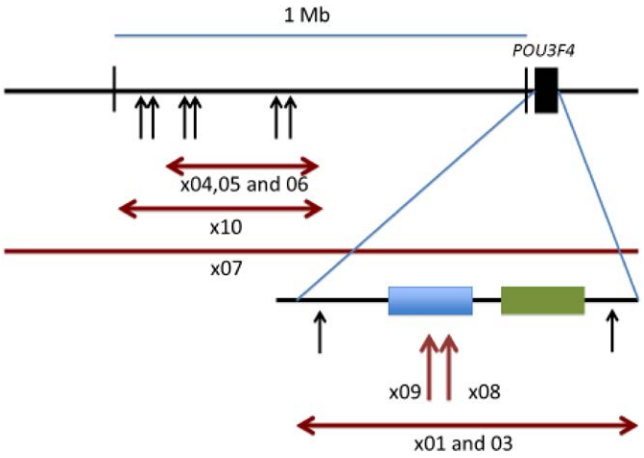

Fig. 1. Location of POU3F4 mutations. Horizontal red bars represent the minimal region of deletions. Vertical red arrows indicate the location of the point mutations. Vertical black arrows represent the location of the MLPA probes.

in Xq21.1q21.31. No mutations were detected by sequencing of *POU3F4*. DNA was unfortunately unavailable for X-inactivation studies.

Hearing and Listening Ability

Visual inspection of the aided FM tone thresholds revealed similar hearing sensitivity between the IP3 malformation and *GJB2* mutation groups, with the largest differences at 6 and 8 kHz (Fig. 2, right and left ears pooled). No statistically significant difference between groups existed for threshold averages of frequencies 0.5, 1, 2, and 4 kHz (IP3 median results: right ear = 39 dB HL, left ear = 34 dB HL; *GJB2* mutations median results: right ear = 36 dB HL, left ear = 38 dB HL, $p > 0.05$). Large variability existed in speech recognition and sound localization performance in both groups (Table 4). All children showed higher speech recognition in quiet than in noise. Speech recognition was significantly higher in the *GJB2* mutation group than in the IP3 group, under both quiet ($Z = -2.5$, $p = 0.02$, $r = 0.52$) and noisy conditions ($Z = -2.1$, $p = 0.04$, $r = 0.53$), while sound localization performance was comparable between groups ($p > 0.05$).

Spoken Language Abilities

Expressive Vocabulary • Children with IP3 malformation had a statistically significantly poorer stanine score on BNT ($Z = -2.33$, $p = 0.02$, $r = 0.54$) as well as raw scores ($Z = -2.10$, $p = 0.04$, $r = 0.44$) (Fig. 3 and Table 4).

Speech Intelligibility

A statistically significant poorer SIR-2 was found in the IP3 malformation group ($Z = -2.80$, $p = 0.01$, $r = 0.41$) (Table 4).

Pragmatic Skills

Results with the parental report of pragmatic skills (CCC-2) revealed three significant differences; first, General Communication Composite score (IGK) ($Z = -2.41$, $p = 0.02$, $r = 0.53$) and second, two subscales, namely coherence ($Z = -2.54$, $p = 0.01$, $r = 0.59$) and use of context ($Z = -2.74$, $p = 0.01$, $r = 0.68$). Semantics and initiative subscales were close to significant ($p > 0.05$) (Fig. 4).

Word Fluency Tasks

No significant differences were found between groups, neither for the phonologically nor semantically based word fluency tasks ($p > 0.05$) (Table 4).

Expressive Grammar

No statistically significant differences were found between groups ($p > 0.05$) (Table 4).

Cognition

Nonverbal Cognitive Ability • No statistically significant differences were found between groups with the Ravens colored matrices ($p > 0.05$) (Table 5).

Cognitive Functioning/Developmental Quotient

A structured observation of children younger than 6 years with the Bayley-II) was done. Several of the children were not co-operative, and therefore, it was not possible to count the raw scores on the Bayley-III and compare with norm data and therefore a comparison between groups was not possible. Observational data for individual children are presented in Appendix 2 in Supplemental Digital Content 1, http://links.lww.com/EANDH/A836. Children older than 6 years old were assessed by EBA-R (IP3 group; n = 6 and *GJB2* mutation controls; n = 4), which is discussed below.

Executive Functioning

Only four children in each group (IP3 and *GJB2* mutations) completed TEA-Ch due to fatigue or other reasons. Despite the small number of children, one statistically significant difference was found on one subscale: Spacehunt-TIME ($Z = -2.34$, $p = 0.02$, $r = 0.78$) indicating a possible slower processing ability in children with IP3 malformation deafness compared to controls. Data are not shown as there were so few participants that completed this section of the study.

Parent and teacher reports on executive functioning in everyday settings (BRIEF-P and BRIEF) revealed some group-specific differences (Table 5 and Fig. 5). For the global executive composite of EF ability a statistically significant difference was found between groups both in parents ($Z = -2.31$, $p = 0.02$, $r = 0.49$) and teachers ($Z = -2.17$, $p = 0.03$, $r = 0.43$). For the BRI, a statistically significant difference was also found between groups for parents ($Z = -2.25$, $p = 0.03$, $r = 0.46$) and close to significant for teachers ($p > 0.05$). For the Metacognition Index, a statistically significant difference was found between parents in the two groups ($Z = -2.82$, $p = 0.01$, $r = 0.72$) but not between teachers ($p > 0.05$). Statistically significant differences between groups were found on three individual subscales for parents; emotional control ($Z = -2.59$, $p = 0.01$, $r = 0.61$), initiate ($Z = -2.29$, $p = 0.02$, $r = 0.48$), and working memory ($Z = -2.27$, $p = 0.02$, $r = 0.47$) (Fig. 5).

Phonological and General Working Memory

Children with IP3 malformation had statistically significantly lower scores than controls on the phonological working memory task (Serial recall of nonsense word-2) ($Z = -2.08$, $p = 0.04$, $r = 0.62$) 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 GJB2 mutations ($Z = -2.68$, $p = 0.01$, $r = 0.72$). For example, the response of a child with IP3 malformation when the test

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		
X03*	1	2008	M	Hemizygous deletion of 2 probes in exon1	NP		Obligate carrier
X04†	3	2008	M	Hemizygous deletion of 4 probes upstream	NP	Heterozygous mutation in GJB2 c.[35del];[=]	Obligate carrier
X05‡	3	2008	M	Hemizygous deletion of 4 probes upstream	NP	100kb deletion 500kb upstream (PCR)	Obligate carrier
X06†	3	2009	M	NP	Mutation not detected	Hemizygous deletion upstream (422–622kB)	Obligate carrier
X07	4	2011	F	Heterozygous deletion of 2 probes in exon 1 + deletion of 6 probes upstream	Mutation not detected	Array CGH 8Mb deletion Xq21.1q21.31 (UCSC hg18 ChX:78176502-86386384)	NP
X08	5	2011	M	Mutation not detected	c.704del pPhe235Serfs*6 (POU domain)		NP
X09	6	2013	M	Mutation not detected	c.666_667del p.Tyr223Trpfs*2 (POU domain)	Fragile X normal Array CGH normal	NP
X10	7	2012	M	Hemizygous deletion of 6 probes upstream	NP		NP

*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.

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

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.

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	
							FAS	Animal (Raw Scores)
X01 (9;6)	64	44	0.19	8	5	32/2	21	17
X02 (9;3)	48	20	0.50	7	4	23/1	16	14
X03 (6;9)	48	8	0.56	7	4	14/1	7	7
X04 (6;8)	52	20	0.38	7	3	6/1	12	14
X05 (6;9)	8	*	0.38	7	3	*	*	8
X06 (4;9)	52	20	0.19	7	3	21/1	*	9
X07 (3;6)†				4	2			
X08 (3;6)†				3	2			
X09 (2;0)†				2	1			
X10 (2;9)†				3	2			
Mean	45	24	0.36	6	3	19/1	14	12
SD	19.2	13.1	0.15	2.2	1.2	10.7/0.4	5.9	4.0
Median	50	20	0.38	6	3	21/1	14	11
C01 (14;5)	84	*	0.38	8	5	31/1	18	22
C02 (8;9)	96	56	0.00	8	5	49/9	20	16
C03 (2;0)†				4	3			
C04 (5;8)	64	56	0.88	7	5	23/4	1	9
C05 (3;5)†				7	4			
C06 (1;6)†				6	3			
C07(12;3)	100	68	0.06	8	5	52/9	37	17
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	*	9
Mean	78	53	0.46	7	5	36/5	16	13
SD	19.3	15.1	0.39	1.3	0.9	12.4/3.2	14.0	5.9
Median	84	56	0.40	8	5	33/5	18	14

** Not done because of fatigue or unclear reasons.*
†Not performed because of younger age.

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

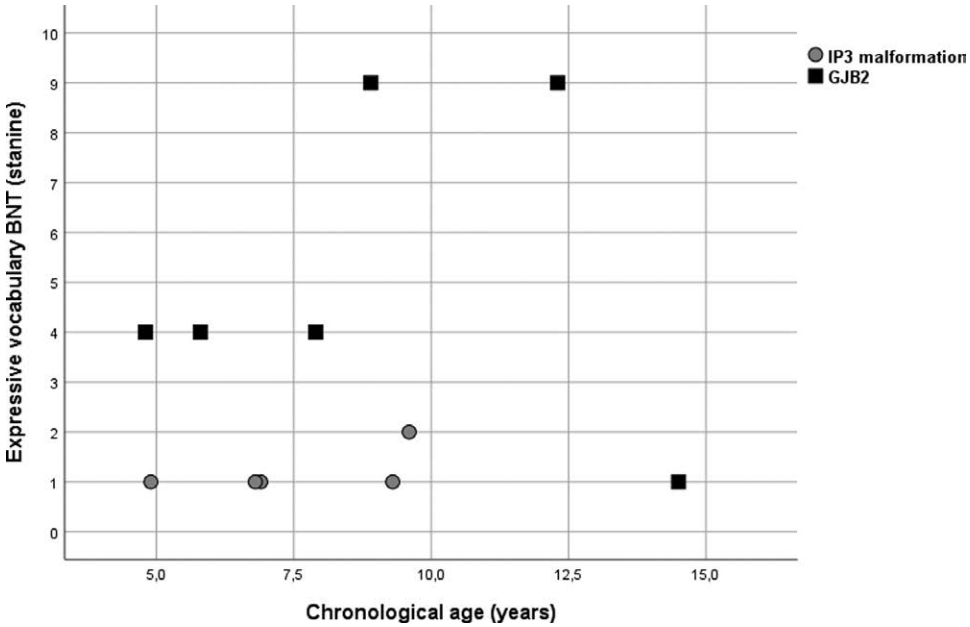

Fig. 3. Expressive vocabulary (BNT). Stanine results for children with IP3 malformation (n = 5) and children with GJB2 in relation to chronological age (n = 6). BNT, Boston Naming Test.

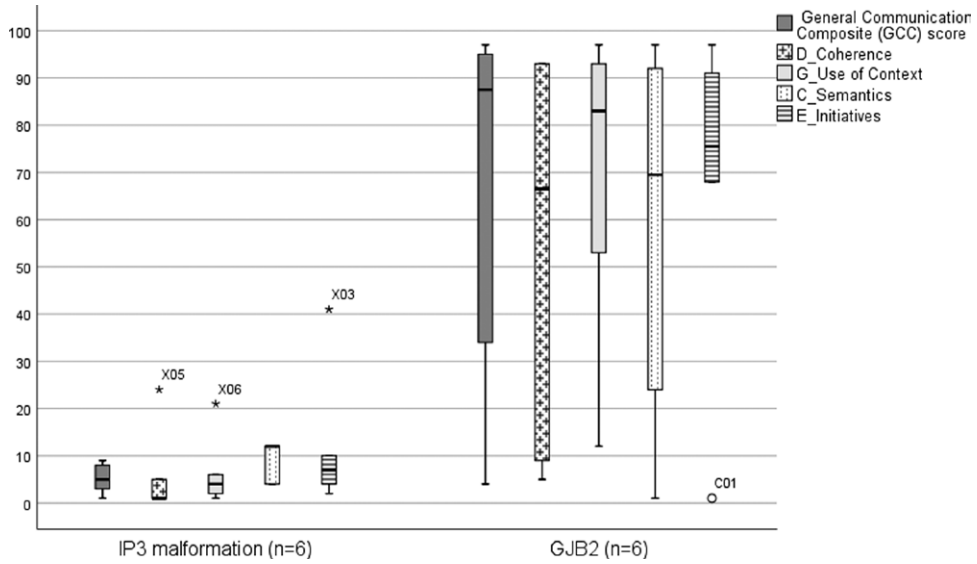

Fig. 4. Pragmatic results (CCC-2). Percentile results for children with IP3 malformation (n = 6) and children with GJB2 (n = 5). GCC score (10 subscales) and results on four individual subscales; coherence, use of context, semantics and initiatives. CCC-2, Children's Communication Checklist-2; GCC, General Communication Composite.

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,

TABLE 5. Cognitive outcome on individual and group level (IP3 malformation and *GJB2*) including nonverbal cognitive ability (Ravens), executive functioning (BRIEF questionnaire for parents and teachers), and two working memory tests, performed in participants older than 4 years (chronological age) (n = 12)

Case Identifier	Nonverbal Cogn.	Executive Functioning						Working Memory	
	Ravens	Parent			Teacher			Sentence	Serial
		BRI	MI	GEC	BRI	MI	GEC	C.	R.
X01	26	65	57	63	70	73	73	9.5	0
X02	34	56	56	56	*	*	*	13.5	†
X03	25	47	57	41	46	44	44	4.5	1.0
X04	22	79	62	70	71	75	72	7.0	0
X05	ND	71	58	65	68	49	67	0	†
X06	23	79	62	70	63	75	72	4.0	1.0
Median	25	68	58	64	68	73	72	6.0	0.5
C01	32	55	52	53	61	68	67	12.5	1.0
C02	35	54	52	53	53	46	48	12.0	18.0
C04	33	49	56	54	58	55	57	6.0	11.0
C07	34	40	43	41	43	42	42	15.5	13.0
C08	14	38	44	41	42	46	41	4.5	†
C10	25	48	42	44	56	55	56	6.5	†
Median	33	49	48	49	55	51	52	9.0	6.0

Nonverbal cognitive ability (Ravens) raw scores, GJB2 (n = 6) and IP3 malformation (n = 5). Executive functioning (BRIEF-P, BRIEF) t-scores for two summative indexes and a composite comprised of eight different subscales; Behavior Regulation Index; Inhibit, Shift, and Emotional control, Metacognition Index; Initiate, Working memory, Plan/Organize, Organization of material and Monitor, and GEC Global Executive Composite (including all subscales) (rated by parents and teachers) in each group (n = 6, respectively, n = 6).
**Teacher rating for X02 is missing due to unclear reason. General working memory (sentence completion) (n = 6; n = 6), respectively, and phonological working memory (serial recall of nonsense words) raw scores on individual level (n = 4; n = 4), respectively.*
†Not done because of fatigue or unclear reasons.

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

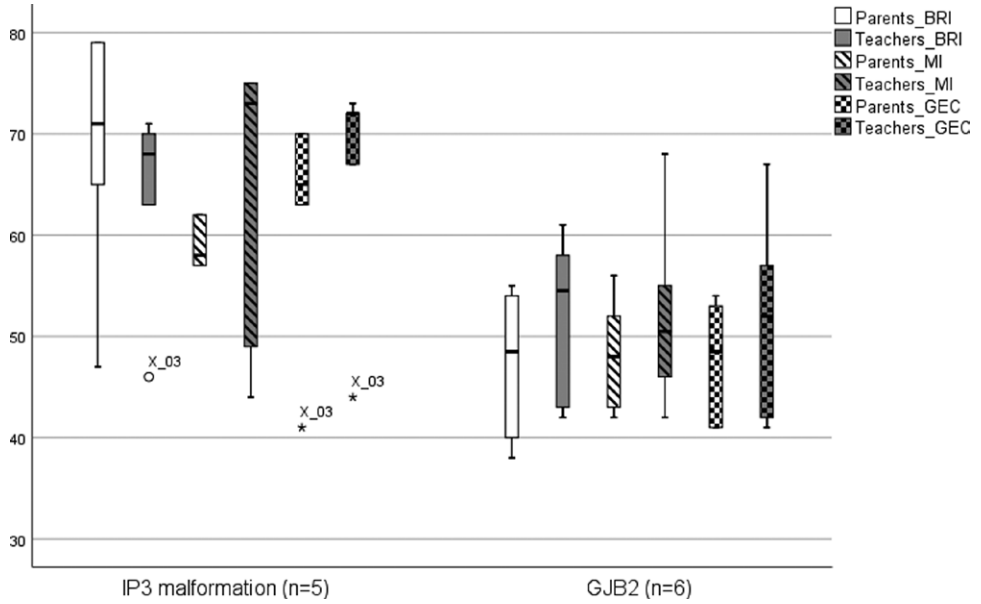

Fig. 5. Executive functions (BRIEF). T-scores (BRI, MI, and GEC) on group level (IP3 malformation; n = 5 and GJB2; n = 6). T-scores over 65 are considered atypical. BRI, Behavioral Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; GEF, global executive composite; IP3, incomplete partition type 3; MI, Metacognition Index.

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 childrens' poor EF led to the exhibited poor attention. Furthermore, phonological working memory which is part of the EF domain was significantly poorer

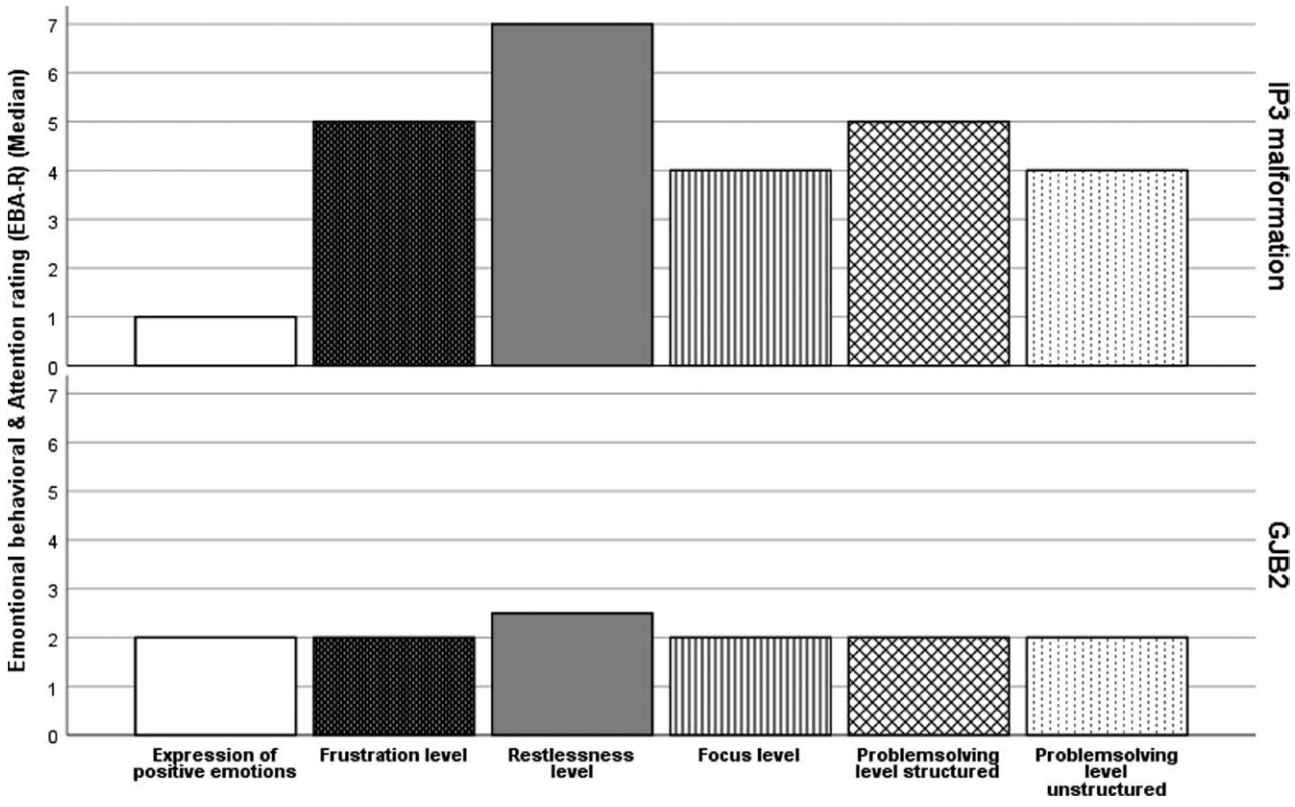

Fig. 6. EBA-R. Median scores on group level (IP3 malformation vs. GJB2) from an Observational Qualitative Analysis rating scale containing six different parameters, performed and rated by a blinded psychologist during the test occasion. EBA-R, Emotional Behavioral Attention Rating; IP3, incomplete partition type 3.

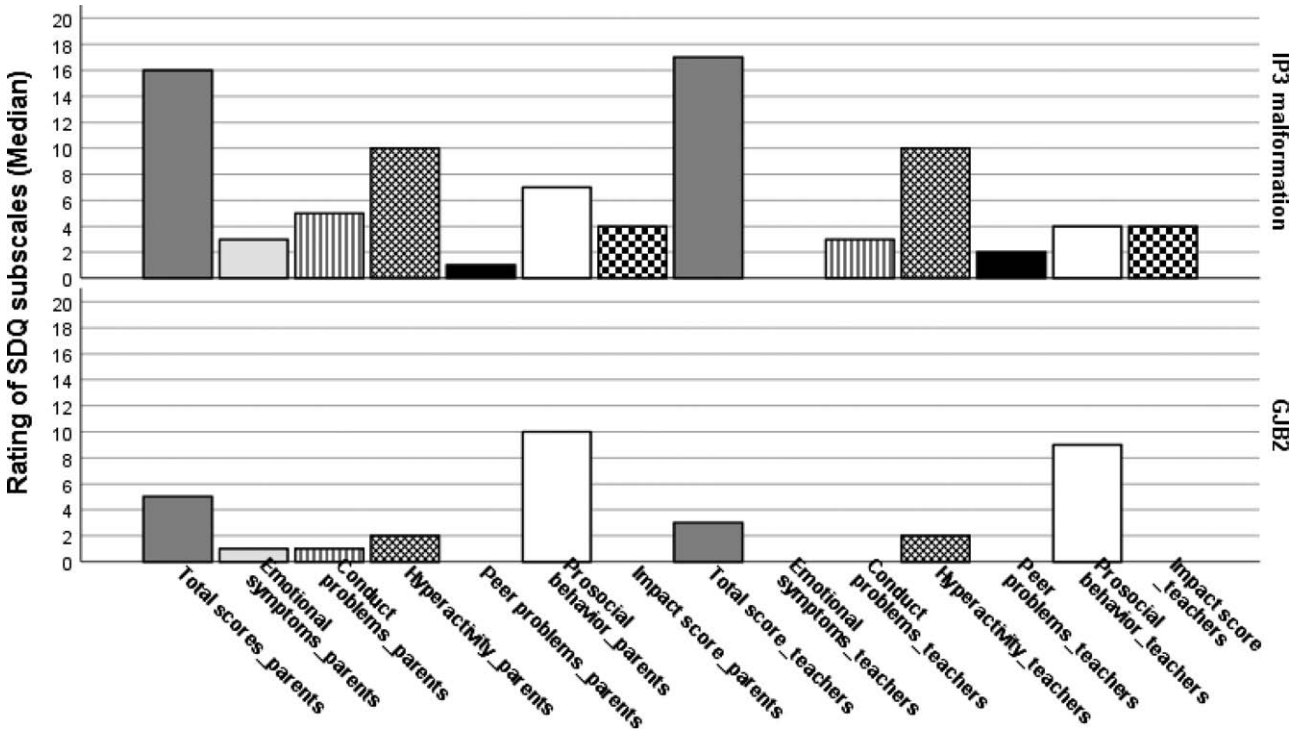

Fig. 7. Mental ill-health (SDQ subscales). Median scores on group level (IP3 malformation and GJB2) from parent ratings. IP3, incomplete partition type 3; SDQ, Strengths and Difficulties Questionnaire.

for children with IP3 malformation than controls. This skill has previously been found to be difficult for children with CI, irrespectively 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

TABLE 6. Number of individuals in both groups (IP3 malformation and *GJB2*) with SDQ-results that indicate (1) borderline behavior or (2) abnormal behavior (Goodman 1999), based on validated cutoff values (Goodman 2005)

	Father Ratings		Mother Ratings		Teacher Ratings	
	IP3	GJB2	IP3	GJB2	IP3	GJB2
SDQ scales	n = 7	n = 7	n = 6	n = 6	n = 6	n = 7
Total difficulties	2:3	1:1	2:6	2:1	1:1,2:3	/
Emotional symptoms	2:2	1:1	1:1,2:1	1:2	/	/
Conduct problems	1:1,2:3	1:1,2:1	1:1,2:3	1:3	1:2,2:2	/
Hyperactivity	1:1,2:4	1:1	1:1,2:4	/	2:4	2:1
Peer problems	1:1,2:1	1:1,2:1	2:1	2:1	/	/
Prosocial behavior	1:1	1:1	/	/	1:1,2:3	2:1
Impact score	1:1,2:4	/	1:1,2:5	/	2:4	1:1
Total	1:5,2:17	1:6,2:2	1:4,2:20	1:5,2:2	1:4,2:16	1:1,2:2

/, only normal results reported; 1, borderline; 2, abnormal impairment; IP3, incomplete partition type 3; SDQ, Strengths and Difficulties Questionnaire.
Children with reported borderline, at least rated once, by parents: X03, 04, 05, 06, 07, 08, and C01, 02, 04, and 05. Abnormal impairment rated at least once by parents: X03, 04, 05, 06, 07, 08, and C01. Borderline rated by teachers at least once: X03, 05, 08, and C04. Abnormal impairment rated at least once by teachers: X03, 05, 06, 08, and C04.

of mental ill-health (Haukedal et al. 2020). However, the presence of *additional disabilities* seen in syndromic cohorts, or acquired deafness with comorbid conditions, are suggested to be risk factors related to mental ill-health and poorer social skills (Haukedal et al. 2020). Children with IP3 malformation exhibited multiple difficulties that were not explained by hearing alone. The three main atypical symptoms in children with IP3 malformation were related to poor outcome on (1) lexical-semantic abilities; (2) pragmatic skills; and (3) a greater *amount* of atypical executive functioning skills, with diagnosed ADHD or suspected ADHD or ASD. Furthermore, these additional deficits and diagnoses were accompanied with a poorer mental ill-health, which previously has been shown in groups with additional diagnoses (Haukedal et al. 2020).

Worse speech recognition in the IP3 malformation group compared to controls (*GJB2*) could explain their poorer speech intelligibility but only partly explains their poorer EF and lexical skills. Participants with IP3 malformation exhibited significantly worse naming ability and poorer expressive vocabulary (BNT) which is not related to hearing alone, considering that the control group had a similar nonverbal cognitive ability (Moog & Geers 2003) and socioeconomic background (Szagun & Stumper 2012). Furthermore, children with IP3 malformation had significantly more semantic irrelevant responses on the general working memory task than controls, which indicates an atypical semantic ability (Löfkvist et al. 2014).

We have previously reported (Löfkvist et al. 2014) that children with CI exhibited semantic *relevant* errors when they named pictures wrongly in the BNT, and that they were on par with age-matched peers with typical hearing. However, children with typical hearing and high-functioning ASD, and a group of children with DLD, exhibited significantly more *atypical* error responses than children with CI. Children with ASD named the picture with semantic irrelevant responses, while children with DLD named fewer pictures. Participants with IP3 malformation in the present study had similar raw scores on the general working memory test as controls, which could reflect adequate cognitive processing skills. However, the error lexical-semantic responses on the general working memory task were significantly more deviant compared to the same responses from controls with *GJB2* mutation, and from previous studies of children with CI (Löfkvist et al. 2014). The irrelevant or more atypical lexical-semantic associations of children with IP3 malformation resembled responses from adults with neurodegenerative diseases (Löfkvist et al. 2014; Löfkvist, Reference Note 4). Additionally, the level of atypical executive functioning skills and behavior problems during the assessment procedures were worse for individuals with IP3 malformation, compared to controls.

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.

Study Limitations

To our knowledge, this is one of the largest reported studies of children with IP3 malformation deafness, where nine patients had a confirmed deletion/mutation in *POU3F4* on the X-chromosome. However, the study group was small and one should therefore be careful when generalizing these results to all children with IP3 or X-linked hearing loss, especially those with milder forms of hearing loss. It should also be noted that the 10 patients represented only six probands as five of these patients were related to a variety of degrees. Therefore, co-inherited traits could affect their behavioral phenotype. Furthermore, several of the tests performed in this study included only six of these individuals, as the patient was required to be of a certain age to perform them. This would introduce a level of bias and further reduce its applicability over the whole IP3 population, as only three probands were included. Nevertheless, we suggest that the different subgroup specific results are representative for those children with severe hearing loss that is related to *POU3F4* mutation or IP3 malformation. Within the control group, the exact mutation in the *GJB2* gene in each individual was not available to the authors.

It is also important to understand that several genes on the X-chromosome are related to attention and EF (Green et al. 2015), as discussed above. These genes were not directly investigated in this study and it is plausible that undetected mutations are present, resulting in a subject affected by two separate conditions. One could also speculate on the presence of a confounding effect from the POU3F4 mutation, especially in the case of X07.

The children in the current study with IP3 malformation deafness had a more significant hearing loss preoperatively when compared to the control group; however, hearing thresholds were similar postoperatively. This bias does not, however, completely explain the behavioral patterns exhibited in these patients as discussed above. Because children with X-linked hearing impairment often have a more severe form of progressive hearing loss and they are referred for cochlear implantation at a later age, it is difficult to provide suitable and matched controls.

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 *POU3F4* 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 perseverance, 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 *POU3F4* 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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REFERENCES

Alballaa, A., Aschendorff, A., Arndt, S., Hildenbrand, T., Becker, C., Hassepass, F., Laszig, R., Beck, R., Speck, I., Wesarg, T., Ketterer, M. C. (2019). Incomplete partition type III revisited-long-term results following cochlear implant. German version. *HNO*, *67*, 760–768.

Allen, C., Nikolopoulos, T. P., Dyar, D., O'Donoghue, G. M. (2001). Reliability of a rating scale for measuring speech intelligibility after pediatric cochlear implantation. *Otol Neurotol*, *22*, 631–633.

Anderson, V. (2002). Executive function in children: Introduction. *Child Neuropsychol*, *8*, 69–70.

Anmyr, L., Larsson, K., Olsson, M., Freijd, A. (2012). Strengths and difficulties in children with cochlear implants–comparing self-reports with reports from parents and teachers. *Int J Pediatr Otorhinolaryngol*, *76*, 1107–1112.

Aschendorff, A., Maier, W., Jaekel, K., Wesarg, T., Arndt, S., Laszig, R., Voss, P., Metzger, M., Schulze, D. (2009). Radiologically assisted navigation in cochlear implantation for X-linked deafness malformation. *Cochlear Implants Int*, *10 Suppl 1*, 14–18.

Asp, F., Eskilsson, G., Berninger, E. (2011). Horizontal sound localization in children with bilateral cochlear implants: Effects of auditory experience and age at implantation. *Otol Neurotol*, *32*, 558–564.

Asp, F., Mäki-Torkko, E., Karltorp, E., Harder, H., Hergils, L., Eskilsson, G., Stenfelt, S. (2012). Bilateral versus unilateral cochlear implants in children: Speech recognition, sound localization, and parental reports. *Int J Audiol*, *51*, 817–832.

Asp, F., & Reinfeldt, S. (2018). Horizontal sound localisation accuracy in individuals with conductive hearing loss: Effect of the bone conduction implant. *Int J Audiol*, *57*, 657–664.

Baddeley, A. (2003). Working memory and language: An overview. *J Commun Disord*, *36*, 189–208.

Baddeley, A. (2012). Working memory: Theories, models, and controversies. *Annu Rev Psychol*, *63*, 1–29.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychol Bull*, *121*, 65–94.

Beer, J., Kronenberger, W. G., Castellanos, I., Colson, B. G., Henning, S. C., Pisoni, D. B. (2014). Executive functioning skills in preschool-age children with cochlear implants. *J Speech Lang Hear Res*, *57*, 1521–1534.

Biederman, J., Kim, J. W., Doyle, A. E., Mick, E., Fagerness, J., Smoller, J. W., Faraone, S. V. (2008). Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD: A preliminary study. *Am J Med Genet B Neuropsychiatr Genet*, *147B*, 1511–1518.

Braunstein, E. M., Crenshaw, E. B. III, Morrow, B. E., Adams, J. C. (2008). Cooperative function of Tbx1 and Brn4 in the periotic mesenchyme is necessary for cochlea formation. *J Assoc Res Otolaryngol*, *9*, 33–43.

Busi, M., Rosignoli, M., Castiglione, A., Minazzi, F., Trevisi, P., Aimoni, C., Calzolari, F., Granieri, E., Martini, A. (2015). Cochlear implant outcomes and genetic mutations in children with ear and brain anomalies. *Biomed Res Int*, *2015*, 696281.

Casserly, E. D., & Pisoni, D. B. (2013). Nonword repetition as a predictor of long-term speech and language skills in children with cochlear implants. *Otol Neurotol*, *34*, 460–470.

Chan, R. C., Shum, D., Toulopoulou, T., Chen, E. Y. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Arch Clin Neuropsychol*, *23*, 201–216.

Choi, B. Y., An, Y. H., Song, J. J., Koo, J. W., Lee, J. H., Oh, S. H., Chang, S. O., Kim, C. S., Park, J. H. (2016). Clinical observations and molecular variables of patients with hearing loss and incomplete partition type III. *Laryngoscope*, *126*, E123–E128.

Coate, T. M., Raft, S., Zhao, X., Ryan, A. K., Crenshaw, E. B. III, Kelley, M. W. (2012). Otic mesenchyme cells regulate spiral ganglion axon fasciculation through a Pou3f4/EphA4 signaling pathway. *Neuron*, *73*, 49–63.

Cole, E. B., & Flexer, C. A. (2020). *Children With Hearing Loss: Developing Listening and Talking, Birth to Six* (4th ed.). Plural Publishing, Inc.

Corvino, V., Apisa, P., Malesci, R., Laria, C., Auletta, G., Franzé, A. (2018). X-linked sensorineural hearing loss: A literature review. *Curr Genomics*, *19*, 327–338.

Cosetti, M. K., Friedmann, D. R., Heman-Ackah, S. E., Perez, R., Waltzman, S. B., Roland, J. T. Jr. (2015). Surgical techniques and outcomes of cochlear implantation in patients with radiographic findings consistent with X-linked deafness. *Int J Pediatr Otorhinolaryngol*, *79*, 1689–1693.

Cosse-Etchepare, C., Gervi, I., Buisson, I., Formery, L., Schubert, M., Riou, J. F., Umbhauer, M., Le Bouffant, R. (2018). Pou3f transcription factor expression during embryonic development highlights distinct pou3f3 and pou3f4 localization in the Xenopus laevis kidney. *Int J Dev Biol*, *62*, 325–333.

Davies, W. (2014). Sex differences in attention Deficit Hyperactivity Disorder: Candidate genetic and endocrine mechanisms. *Front Neuroendocrinol*, *35*, 331–346.

Figueras, B., Edwards, L., Langdon, D. (2008). Executive function and language in deaf children. *J Deaf Stud Deaf Educ*, *13*, 362–377.

Gardner, M. B., & Gardner, R. S. (1973). Problem of localization in the median plane: Effect of pinnae cavity occlusion. *J Acoust Soc Am*, *53*, 400–408.

Gathercole, S. E., Alloway, T. P., Kirkwood, H. J., Elliott, J. G., Holmes, J., Hilton, K. A. (2008). Attentional and executive function behaviours in children with poor working *memory*. *Learn Individ Differ*, *18*, 214–233.

Giannantonio, S., Agolini, E., Scorpecci, A., Anzivino, R., Bellacchio, E., Cocciadiferro, D., Novelli, A., Digilio, M. C., Marsella, P. (2020). Genetic identification and molecular modeling characterization of a novel POU3F4 variant in two Italian deaf brothers. *Int J Pediatr Otorhinolaryngol*, *129*, 109790.

Gioia, G. A., Isquith, P. K., Guy, S. C., et al. (2000). TEST REVIEW: Behavior rating inventory of executive function. *Child Neuropsychol*, *6*, 235–238.

Glick, H., & Sharma, A. (2017). Cross-modal plasticity in developmental and age-related hearing loss: Clinical implications. *Hear Res*, *343*, 191–201.

Gong, W. X., Gong, R. Z., Zhao, B. (2014). HRCT and MRI findings in X-linked non-syndromic deafness patients with a POU3F4 mutation. *Int J Pediatr Otorhinolaryngol*, *78*, 1756–1762.

Goodman, R. (1997). The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry*, *38*, 581–586.

Goodman, R. (1999). The extended version of the strengths and difficulties questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatry*, *40*, 791–799.

Goodman, R. (2005). Youth in Mind, SDQ-Information for Researches and Professionals About the Strengths and Difficulties Questionnaire. http://www.sdqinfo.org/.

Green, T., Bade Shrestha, S., Chromik, L. C., Rutledge, K., Pennington, B. F., Hong, D. S., Reiss, A. L. (2015). Elucidating X chromosome influences on attention deficit hyperactivity disorder and executive function. *J Psychiatr Res*, *68*, 217–225.

Greven, C. U., Kovas, Y., Willcutt, E. G., Petrill, S. A., Plomin, R. (2014). Evidence for shared genetic risk between ADHD symptoms and reduced mathematics ability: A twin study. *J Child Psychol Psychiatry*, *55*, 39–48.

Haukedal, C. L., Lyxell, B., Wie, O. B. (2020). Health-related quality of life with cochlear implants: The Children's perspective. *Ear Hear*, *41*, 330–343.

Haukedal, C. L., von Koss Torkildsen, J., Lyxell, B., Wie, O. B. (2018). Parents' perception of health-related quality of life in children with cochlear implants: The impact of language skills and hearing. *J Speech Lang Hear Res*, *61*, 2084–2098.

Heaton, S. C., Reader, S. K., Preston, A. S., Fennell, E. B., Puyana, O. E., Gill, N., Johnson, J. H. (2001). The Test of Everyday Attention for Children (TEA-Ch): Patterns of performance in children with ADHD and clinical controls. *Child Neuropsychol*, *7*, 251–264.

Henricson, C., Wass, M., Lidestam, B., Möller, C., Lyxell, B. (2012). Cognitive skills in children with Usher syndrome type 1 and cochlear implants. *Int J Pediatr Otorhinolaryngol*, *76*, 1449–1457.

Hintermair, M. (2007). Prevalence of socioemotional problems in deaf and hard of hearing children in Germany. *Am Ann Deaf*, *152*, 320–330.

Huber, M., & Kipman, U. (2011). The mental health of deaf adolescents with cochlear implants compared to their hearing peers. *Int J Audiol*, *50*, 146–154.

Incesulu, A., Adapinar, B., Kecik, C. (2008). Cochlear implantation in cases with incomplete partition type III (X-linked anomaly). *Eur Arch Otorhinolaryngol*, *265*, 1425–1430.

Isquith, P. K., Gioia, G. A., Espy, K. A. (2004). Executive function in preschool children: Examination through everyday behavior. *Dev Neuropsychol*, *26*, 403–422.

Kang, W. S., Shim, B. S., Lee, K. S. (2013). Audiologic performance after cochlear implantation in children with X-linked deafness: Comparison with deaf children with a normal inner ear structure. *Otol Neurotol*, *34*, 544–548.

Kent, L., Emerton, J., Bhadravathi, V., Weisblatt, E., Pasco, G., Willatt, L. R., McMahon, R., Yates, J. R. (2008). X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits. *J Med Genet*, *45*, 519–524.

Kim, C. S., Maxfield, A. Z., Foyt, D., Rapoport, R. J. (2018). Utility of intraoperative computed tomography for cochlear implantation in patients with difficult anatomy. *Cochlear Implants Int*, *19*, 170–179.

Kim, L., Wisely, C. E., Lucius, S., Weingarten, J., Dodson, E. E. (2016). Positive outcomes and surgical strategies for bilateral cochlear implantation in a child with X-linked deafness. *Ann Otol Rhinol Laryngol*, *125*, 173–176.

Kral, A., Kronenberger, W. G., Pisoni, D. B., O'Donoghue, G. M. (2016). Neurocognitive factors in sensory restoration of early deafness: A connectome model. *Lancet Neurol*, *15*, 610–621.

Kronenberger, W. G., Colson, B. G., Henning, S. C., Pisoni, D. B. (2014). Executive functioning and speech-language skills following long-term use of cochlear implants. *J Deaf Stud Deaf Educ*, *19*, 456–470.

Kronenberger, W. G., Pisoni, D. B., Henning, S. C., Colson, B. G. (2013). Executive functioning skills in long-term users of cochlear implants: A case control study. *J Pediatr Psychol*, *38*, 902–914.

Kronenberger, W. G., Xu, H., Pisoni, D. B. (2020). Longitudinal development of executive functioning and spoken language skills in preschool-aged children with cochlear implants. *J Speech Lang Hear Res*, *63*, 1128–1147.

Lee, H. K., Lee, S. H., Lee, K. Y., Lim, E. J., Choi, S. Y., Park, R. K., Kim, U. K. (2009). Novel POU3F4 mutations and clinical features of DFN3 patients with cochlear implants. *Clin Genet*, *75*, 572–575.

Loe, I. M., & Feldman, H. M. (2007). Academic and educational outcomes of children with ADHD. *Ambul Pediatr*, *7*(1 Suppl), 82–90.

Löfkvist, U., Almkvist, O., Lyxell, B., Tallberg, I. M. (2012). Word fluency performance and strategies in children with cochlear implants: Age-dependent effects? *Scand J Psychol*, *53*, 467–474.

Löfkvist, U., Almkvist, O., Lyxell, B., Tallberg, I. M. (2019). Lexical and semantic ability in groups of children with cochlear implants, language impairment and autism spectrum disorder. *Int J Pediatr Otorhinolaryngol*, *78*, 253–263.

Löfkvist, U., Anmyr, L., Henricson, C., Karltorp, E. (2020). Executive functions, pragmatic skills, and mental health in children with congenital cytomegalovirus (CMV) infection with cochlear implants: A pilot study. *Front Psychol*, *10*, 2808.

Lyxell, B., Wass, M., Sahlén, B., Samuelsson, C., Asker-Arnason, L., Ibertsson, T., Mäki-Torkko, E., Larsby, B., Hällgren, M. (2009). Cognitive development, reading and prosodic skills in children with cochlear implants. *Scand J Psychol*, *50*, 463–474.

Malmberg, M., Rydell, A. M., Smedje, H. (2003). Validity of the Swedish version of the Strengths and Difficulties Questionnaire (SDQ-Swe). *Nord J Psychiatry*, *57*, 357–363.

Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., Robertson, I. H. (2001). The differential assessment of children's attention: The Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *J Child Psychol Psychiatry*, *42*, 1065–1081.

Marlin, S., Moizard, M. P., David, A., Chaissang, N., Raynaud, M., Jonard, L., Feldmann, D., Loundon, N., Denoyelle, F., Toutain, A. (2009). Phenotype and genotype in females with POU3F4 mutations. *Clin Genet*, *76*, 558–563.

Minowa, O., Ikeda, K., Sugitani, Y., Oshima, T., Nakai, S., Katori, Y., Suzuki, M., Furukawa, M., Kawase, T., Zheng, Y., Ogura, M., Asada, Y., Watanabe, K., Yamanaka, H., Gotoh, S., Nishi-Takeshima, M., Sugimoto, T., Kikuchi, T., Takasaka, T., Noda, T. (1999). Altered cochlear fibrocytes in a mouse model of DFN3 nonsyndromic deafness. *Science*, *285*, 1408–1411.

Moog, J. S., & Geers, A. E. (2003). Epilogue: Major findings, conclusions and implications for deaf education. *Ear Hear*, *24*(1 Suppl), 121S–125S.

Petersen, M. B., Wang, Q., Willems, P. J. (2008). Sex-linked deafness. *Clin Genet*, *73*, 14–23.

Saeed, H., Powell, H. R., Saeed, S. R. (2016). Cochlear implantation in X-linked deafness - How to manage the surgical challenges. *Cochlear Implants Int*, *17*, 178–183.

Sennaroğlu, L., & Bajin, M. D. (2018). Incomplete partition type III: A rare and difficult cochlear implant surgical indication. *Auris Nasus Larynx*, *45*, 26–32.

Sennaroglu, L., Sarac, S., Ergin, T. (2006). Surgical results of cochlear implantation in malformed cochlea. *Otol Neurotol*, *27*, 615–623.

Smedje, H., Broman, J. E., Hetta, J., von Knorring, A. L. (1999). Psychometric properties of a Swedish version of the "Strengths and Difficulties Questionnaire". *Eur Child Adolesc Psychiatry*, *8*, 63–70.

Smeds, H., Wales, J., Asp, F., Löfkvist, U., Falahat, B., Anderlid, B. M., Anmyr, L., Karltorp, E. (2017). X-linked malformation and cochlear implantation. *Otol Neurotol*, *38*, 38–46.

Stankovic, K. M., Hennessey, A. M., Herrmann, B., Mankarious, L. A. (2010). Cochlear implantation in children with congenital X-linked deafness due to novel mutations in POU3F4 gene. *Ann Otol Rhinol Laryngol*, *119*, 815–822.

Szagun, G., & Stumper, B. (2012). Age or experience? The influence of age at implantation and social and linguistic environment on language development in children with cochlear implants. *J Speech Lang Hear Res*, *55*, 1640–1654.

Tallberg, I. M. (2005). The Boston Naming Test in Swedish: Normative data. *Brain Lang*, *94*, 19–31.

Tallberg, I. M., Carlsson, S., Lieberman, M. (2011). Children's word fluency strategies. *Scand J Psychol*, *52*, 35–42.

Teagle, H. F., Roush, P. A., Woodard, J. S., Hatch, D. R., Zdanski, C. J., Buss, E., Buchman, C. A. (2010). Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear*, *31*, 325–335.

Tian, H., Wang, L., Gao, F., Liang, W., Peng, K. A. (2018). Cochlear implantation using a custom guide catheter in 14 patients with incomplete partition type III. *Clin Otolaryngol*, *43*, 1379–1383.

Tranebjaerg, L., Schwartz, C., Eriksen, H., Andreasson, S., Ponjavic, V., Dahl, A., Stevenson, R. E., May, M., Arena, F., Barker, D. (1995). A new X linked recessive deafness syndrome with blindness, dystonia, fractures, and mental deficiency is linked to Xq22. *J Med Genet*, *32*, 257–263.

Van Camp, G., & Smith, R. (2019). Hereditary hearing loss, University of Antwerp. http://hereditaryhearingloss.org.

Walker, E. A., McCreery, R. W., Spratford, M., Oleson, J. J., Van Buren, J., Bentler, R., Roush, P., Moeller, M. P. (2015). Trends and predictors of longitudinal hearing aid use for children who are hard of hearing. *Ear Hear*, *36*(Suppl 1), 38S–47S.

Wester, J. L., Merna, C., Peng, K. A., Lewis, R., Sepahdari, A. R., Ishiyama, G., Hosokawa, K., Kumakawa, K., Ishiyama, A. (2016). Facial nerve stimulation following cochlear implantation for X-linked stapes gusher syndrome leading to identification of a novel POU3F4 mutation. *Int J Pediatr Otorhinolaryngol*, *91*, 121–123.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biol Psychiatry*, *57*, 1336–1346.

Willstedt-Svensson, U., Löfqvist, A., Almqvist, B., Sahlén, B. (2004). Is age at implant the only factor that counts? The influence of working memory on lexical and grammatical development in children with cochlear implants. *Int J Audiol*, *43*, 506–515.

Xu, X., Brookes, K., Sun, B., Ilott, N., Asherson, P. (2009). Investigation of the serotonin 2C receptor gene in attention deficit hyperactivity disorder in UK samples. *BMC Res Notes*, *2*, 71.

REFERENCE NOTES

1. Bayley, N. (2006). *Bayley Scales of Infant and Toddler Development, Third Edition: Administration Manual*. Harcourt.
2. Bishop, D. V. M. (2003). *The Children's Communication Checklist Version 2 (CCC-2)*. Psychological Corporation.
3. Kaplan, E. F., Goodglass, H., Weintraub, S. (1983). *The Boston Naming Test* (2nd ed.). Lea & Febiger, Philadelphia.
4. Löfkvist, U. (2014). *Lexical Semantic Development in Children with Cochlear Implants* (*thesis)*. Karolinska Institute.
5. Raven, J., Raven, J. C., Court, J. H. (2003). *Manual for Raven's Progressive Matrices and Vocabulary Scales*. Pearson Assessment.
6. Wass, M. (2009). *Children with Cochlear Implants - Cognition and Reading Ability* (*thesis)*. Linköping University.