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Cognitive, neurological and behavioral features in adults with *KCNJ11* neonatal diabetes

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Abstract

Objective—Central nervous system (CNS) features in children with permanent neonatal diabetes (PNDM) due to *KCNJ11* mutations have a major impact on affected families. Sulfonylurea therapy achieves outstanding metabolic control, but only partial improvement in CNS features. The effects of *KCNJ11* mutations on the adult brain and their functional impact are not well described. We aimed to characterise the CNS features in adults with *KCNJ11* PNDM, compared to adults with *INS* PNDM.

Research Design and Methods—Adults with PNDM due to *KCNJ11* mutations (n=8) or *INS* mutations (n=4) underwent a neurological examination, and completed standardised neuropsychological tests/questionnaires about development/behavior. Four individuals in each group underwent a brain MRI scan. Test scores were converted to Z-scores using normative data, and outcomes compared between groups.

Results—In individuals with *KCNJ11* mutations, neurological examination was abnormal in 7/8; predominant features were subtle deficits in coordination/motor sequencing. All had delayed developmental milestones and/or required learning support/special schooling. Half had features and/or a clinical diagnosis of autism spectrum disorder. *KCNJ11* mutations were also associated with impaired attention, working memory and perceptual reasoning, and reduced IQ (median IQ *KCNJ11* vs *INS* mutations 76 vs 111, p=0.02). However, no structural brain abnormalities were noted on MRI. The severity of these features was related to the specific mutation and they were absent in individuals with *INS* mutations.

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Conclusions—*KCNJ11* PNDM is associated with specific CNS features which are not due to long-standing diabetes, persist into adulthood despite sulfonylurea therapy, and represent the major burden from *KCNJ11* mutations.

Introduction

KCNJ11 gene mutations are the commonest cause of permanent neonatal diabetes (PNDM), which presents in the first 6 months of life and affects 1 in 100,000 live births (1). *KCNJ11* is expressed in the pancreas and brain as well as other tissues, and encodes the Kir6.2 subunit of the ATP-dependent potassium (K_{ATP}) channel. In the pancreas, the K_{ATP} channel links increasing blood glucose to insulin secretion, but activating *KCNJ11* mutations prevent channel closure in response to metabolically generated ATP and result in diabetes (2). Clinically, patients present in an insulin-deficient state and prior to discovery of disease-causing variants in the *KCNJ11* gene they required insulin therapy. It was later shown that *KCNJ11* PNDM could be treated with sulfonylurea tablets, which bind and close the channel allowing insulin secretion, excellent metabolic control and reduced glycaemic variability (3). For many patients and their families transferring from insulin to oral sulfonylureas vastly improved quality of life in relation to their diabetes (4).

Central nervous system (CNS) features occur in children with *KCNJ11* PNDM in addition to diabetes. These are thought to result from expression of aberrant K_{ATP} channels in the brain. The precise role(s) of K_{ATP} channels in the human CNS has not been fully elucidated, but rodent studies suggest that they play a role in glucose sensing and homeostasis as well as seizure propagation (5; 6). *KCNJ11* is expressed in many brain areas but there are particularly high levels of expression in the cerebellum (7; 8). The cerebellum is well known for its role in motor learning and coordination (9), but it also has functions relating to language, executive function and to mood; furthermore, cerebellar abnormalities have been linked with autism (10; 11). Documented CNS features in children with *KCNJ11* mutations range from subtle neuropsychological impairments that specifically affect attention, praxis and executive function to the severe and overt DEND/intermediate DEND syndrome (developmental delay, epilepsy and neonatal diabetes) (12–15). Other associated features may include psychiatric morbidity, specifically neurodevelopmental disorders and anxiety disorders, visuomotor impairments, and sleep disturbance (16–18). The severity of the CNS phenotype is related to the genotype. For example, the V59M mutation is frequently associated with iDEND syndrome and neurodevelopmental features whereas the R201H mutation, previously associated with diabetes alone, has been more recently linked with subtle neuropsychological features (12). Historically, the severity of CNS features was thought to be related to the functional severity of the specific mutation *in vitro,* although functional interpretation also has to take into account the impact of the mutation on the open probability of the K_{ATP} channel which will depend on whether it affects channel gating or ATP binding (19–22).

Sulfonylurea treatment results in partial improvement in the CNS features (23–26), and resolution of functional cerebellar and temporal lobe abnormalities on single-photon emission computed tomography (SPECT) scanning (24; 27). The improvement in CNS features may be limited as a result of poor penetration of the sulfonylurea across the blood

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brain barrier or active transport back out of the brain, leading to sub-therapeutic concentrations in the cerebrospinal fluid (CSF) (28). This, and anecdotal clinical experience of greater CNS response with higher doses of sulfonylurea, has prompted clinical recommendations of glyburide doses of ~1mg/kg/day in people with severe neurological features secondary to *KCNJ11* mutations (29). However, the neurobehavioral features continue to have a huge impact on families despite sulfonylurea treatment (16). This contrasts markedly with the outstanding metabolic response that changed lives by alleviating the anxiety associated with poor metabolic control (4). A key question is whether the CNS features continue to represent the major burden from *KCNJ11* mutations in adult life. To date all studies characterising CNS features in *KCNJ11* PNDM have been conducted in predominantly paediatric cohorts (12–14; 16; 23). However, brain development continues beyond childhood and adolescence (30; 31). No study has comprehensively assessed the CNS outcomes in adults with *KCNJ11* mutations.

Mutations in the *INS* gene are a less common cause of neonatal diabetes, accounting for around 10% of cases (1). Heterozygous dominant negative *INS* mutations often affect protein synthesis resulting in production of structurally abnormal preproinsulin and proinsulin within the beta cell, endoplasmic reticulum (ER) stress and cell death. Individuals with these mutations also typically present with insulin deficiency, but unlike *KCNJ11* PNDM, require lifelong treatment with replacement doses of insulin (32). The *INS* gene is not expressed in any significant levels in the brain, therefore it is very unlikely that individuals with *INS* mutations would display a characteristic CNS phenotype as a direct result of their mutations (33). In fact, there have not been any reports of any such neurological issues, in contrast to those with *KCNJ11* PNDM.

Individuals with PNDM may have long-term CNS sequelae secondary to diabetic ketoacidosis at diagnosis, as seen in Type 1 diabetes (34; 35). However, cerebral oedema in *KCNJ11* PNDM gives rise to a pattern of neurological impairment distinct from that seen as a direct result of brain K_{ATP} channel dysfunction (36). More subtle neurocognitive problems also occur in the presence of diabetes per se, particularly if metabolic control is poor and diabetes is diagnosed before age 7 (37). Further, individuals with Type 2 diabetes are at increased risk of developing Alzheimer's disease in later life, and this may be in part due to chronic metabolic disturbance and changes in insulin signalling (38). Indeed, there is evidence from both animal and human studies that insulin plays a key role in central processes including memory and learning (38). The non-specific diabetes-related cognitive features could confound assessment of CNS phenotype in people with *KCNJ11* mutations, however people with *INS* mutations are well placed to control for them. There has been no previous detailed comparison of the CNS phenotype in people with *INS* and *KCNJ11* mutations.

Aims

The aims of the study were to characterise the neurological and neuropsychological features in adults with *KCNJ11* PNDM, and to compare these with adults with *INS* PNDM.

Methods

Ethical approval

Ethical approval was obtained from the National Research Ethics Service Committee South West-Exeter.

Sample size and patient recruitment

We identified 34 patients >16 years old with *KCNJ11* mutations and 9 patients >16 years old with *INS* mutations who had received a molecular genetic diagnosis in Exeter and who had been diagnosed with permanent neonatal diabetes under 6 months of age. We approached potential participants either directly at a neonatal diabetes family event in Exeter or via the Consultants in charge of their clinical care. We invited 17 individuals with *KCNJ11* mutations to join the study; of these, 10 agreed to participate. However, 2 individuals were excluded from the analysis due to possible confounding factors: one individual (mutation L164P) was excluded because he was taking antipsychotic medication to treat a psychotic illness at the time of the study and had had a particularly severe initial presentation with diabetic ketoacidosis and 3 days in a coma, and a second individual (mutation V59M) was excluded due to severe neurological impairment following initial presentation with diabetic ketoacidosis (further clinical characteristics of excluded participants are available in online supplemental Table S1). We approached 9 individuals with *INS* mutations and 4 agreed to take part. All participants were from the UK apart from one who was from Canada.

Tests

All participants were visited at home or assessed in the Exeter Clinical Research Facility by the same Consultant neurologist and Consultant clinical neuropsychologist who carried out the history taking using a standard proforma, neurological examination, neuropsychological assessments, mood questionnaire and neurodevelopmental screen. If possible an informant or carer was also present to facilitate information gathering. The severity of intellectual impairment and behavioral disturbance in one individual (*KCNJ11-8* [V59M]) meant that it was not possible for him to attempt any of the cognitive tests. Another individual (*KCNJ11-6* [V252G]) did not wish to attempt the Controlled Oral Word Association Test (COWAT) and was unable to understand instructions for the Colour Trails Test (CTT). In 8 participants (4 with *KCNJ11* mutations and 4 with *INS* mutations), T2-weighted brain magnetic resonance imaging (MRI) scans were performed using a 1.5T MRI scanner. The scans were reviewed and interpreted by a radiologist and a neurologist who were blinded to the mutation status of the individuals concerned.

Medical / developmental history, educational and professional attainment— Participants and informants were asked for a standard medical history, the ages at which major milestones were attained, whether learning support was required and level of education / employment.

Neurological Examination—A full neurological examination was performed. This included assessment of cranial nerves, limb tone, power, reflexes, coordination, sensation, and simple tests of motor sequencing and praxis, comprising 2 tests of bimanual

coordination, one unilateral motor sequencing task (the Luria three hand position test), copying unfamiliar hand positions and manual miming, both tested in each hand.

Psychiatric and neurodevelopmental screen—Current psychological distress was assessed using the Hospital Anxiety and Depression Scale (HADS) questionnaire. The Autism Spectrum Quotient (AQ) was administered to screen for autistic traits.

Cognitive function—A battery of neuropsychological tests were administered to assess a variety of cognitive domains. The Wechsler Abbreviated Scale of Intelligence (WASI) was used as a brief measure of current IQ. The Verbal Paired Associates and Visual Reproduction subtests of the Wechsler Memory Scale (WMS-IV) were used to give a verbal and non-verbal (visual) measure of memory. Subtests of the Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV) were administered: cancellation to assess processing speed and digit span (forwards and backwards) to assess working memory. Subtests of the Visual Object and Space Perception battery (VOSP) assessed visuospatial function; incomplete letters and object decision to test object perception, and dot counting and cube analysis to test spatial perception. The Controlled Oral Word Association Test (COWAT) was used to assess aspects of executive function including verbal fluency, self-monitoring and ability to assimilate and adhere to stipulated rules. The Colour Trails Test (CTT) 1 and 2 were used as measures of sustained and divided attention, hand eye motor coordination and speed. Finally, the Addenbrooke's Cognitive Examination-Revised (ACE-R) was used as a broad screening measure of cognition, providing an assessment of the following cognitive domains; attention/orientation, memory, fluency, language, and visuospatial function.

Functional assessment—The Cambridge Behavioral Inventory Revised (CBI-R) questionnaire was used to complement the information obtained from the history taking. This measure seeks the opinion of the informant e.g. carer or family member on the frequency of a range of behaviors in the domains of memory and orientation, everyday skills, self-care, abnormal behavior (e.g. tactlessness, impulsiveness), mood, unusual beliefs, altered eating habits, disturbed sleep, stereotypic and motor behaviors, and altered motivation. For each behavior the informant assigned a score of 0-4 based on the frequency: scores of 3 (occurring daily) or 4 (occurring constantly) denote a significant behavioral deficit.

Statistical analysis

Data were analysed using Excel 2010 and Stata 14. Qualitative data were presented descriptively. Where population normative data were available, neuropsychological test scores were converted to Z-scores. For VOSP subtests, a pass was a score ≥5th population percentile. To compare characteristics and outcomes between the *KCNJ11* and *INS* groups, data were analysed using non-parametric methods (Mann-Whitney test for numerical variables and Fisher's exact test for categorical variables). Data are presented as median (range) unless otherwise stated.

Results

Participant Characteristics

Baseline clinical characteristics of the participants are outlined in Table 1; these were similar between individuals with *KCNJ11* mutations and individuals with *INS* mutations.

Neurological Features

Abnormalities on neurological examination were identified in 7/8 *KCNJ11* participants and only one *INS* participant (Table 2).

Developmental History, Educational and Professional Attainment

Developmental histories, level of educational support and employment history reported for each participant are described in Table 2. Developmental delay and / or learning difficulties were present in all *KCNJ11* participants and they continued to require high levels of support as adults. In contrast, the *INS* group did not report major learning difficulties in keeping with their subsequent employment history and independence in adulthood.

Neurodevelopmental and Psychiatric Features

4/8 with *KCNJ11* mutations, but none of the participants with *INS* mutations, had features of autistic spectrum disorder, either via a clinical diagnosis of autism or an AQ score at or above the threshold suggestive of clinically significant autistic traits (Table 2 and S3). Two individuals in the *KCNJ11* group and one in the *INS* group required treatment either at the time of the study or in the past for depression or anxiety. HADS scores for anxiety and depression were similar in *KCNJ11* vs *INS* participants (Table S3). One individual in the *KCNJ11* group and 2 individuals in the *INS* group scored above the HADS clinical threshold (11) for anxiety (Table 2, Table S3).

Cognitive Function

IQ was lower in the *KCNJ11* group vs the *INS* group (IQ 76(55-101), n=7 and 111(90-124), n=4, p=0.02). Three individuals in the *KCNJ11* group had IQs <70 (Table S2) and impairments in adaptive behaviors in-keeping with a clinical diagnosis of intellectual disability (39). 5/7 individuals in the *KCNJ11* group scored below the clinical cut-point for cognitive impairment on the ACE-R (Figure S1). CTT1 scores suggested reduced attention (CTT1 Z-score -1.7(-3.0- -0.1), n=6 vs 0.4(-1.1-1.2), n=4, p=0.03, CTT2 Z-score -0.8(-3.0-0.8), n=6 vs. 0.7(-1.0-1.2), n=4, p=0.13 (Figure 2, Table S2)).

In the *KCNJ11* group but not the *INS* group median scores in the *WASI, WAIS* and *WMS* were below population average in all subtests apart from the verbal paired associates subtest of the WMS (Figure 1). Scores were particularly low (≤2SD below population average) in the matrix reasoning component of the WASI (Z-score -3.2(-4.8- -0.9) vs. 0.6(-0.7-0.8), p=0.008) and the digit span component of the WAIS-IV (Z-score -2.0(-3.0-0.3) vs 0(-1.0-0.3), p=0.046). Cancellation scores, although not as markedly reduced compared to population norms, were significantly lower in the *KCNJ11* group (Z-score -1(-3-0) vs 2.8(0.7-3.0), p=0.007). COWAT and VOSP scores showed a trend towards reduced executive

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function and visuospatial function respectively in the *KCNJ11* group (Table S3), although these did not reach statistical significance.

Behavioral / functional impact

In the *KCNJ11* group, 6 individuals had severe behavioral features which clustered in the domains of everyday skills (5/6), stereotypic behavior (5/6), memory and orientation (4/6), abnormal behavior (3/6), mood (3/6), and motivation (3/6). Specific everyday skills highlighted included writing (3/5) and dealing with money/bills (2/5). The most frequent stereotypic behaviors were being rigid / fixed (3/5) and having fixed routines (4/5). Poor concentration was highlighted as a specific feature in all 4 individuals who had memory and orientation problems. Two individuals had significant difficulties with self-care and 2 reported disturbed sleep.

Neuroimaging

Structural brain MRI was normal in participants with *KCNJ11* mutations. In *INS* controls, 2 were normal, and 2 had minor abnormalities which were not clinically significant (Table 2).

Severity of impairments associated with the specific mutation

Performance in the cognitive tests was better in the 2 individuals with the R201H mutation. These individuals consistently had scores equal to or greater than the *KCNJ11* group medians (Figures 1 and 2, Table S2), and no significant behavioral features were reported.

Discussion

We have characterised for the first time the profile of neurological, neuropsychological and behavioral features present in adults with PNDM due to *KCNJ11* mutations. The key features were learning difficulties, features of ASD, subtle motor deficits affecting coordination and motor sequencing, and reduced IQ. Specific cognitive domains most affected were perceptual/non-verbal reasoning, working memory, and attention, with a trend towards executive dysfunction and impaired visuospatial abilities. Verbal paired associate memory was relatively preserved. The impact on everyday functioning was significant; 2 participants were severely impaired, requiring support with activities of daily living. A comparison group of patients with neonatal diabetes of similar duration due to *INS* mutations did not show any of these specific features indicating that they are unlikely to be a non-specific effect of metabolic disturbance from birth. Furthermore, as both groups were insulin treated from diagnosis as infants, the differences observed are unlikely to have been influenced by variation in the timing or duration of action of insulin on insulin and IGF receptors in the brain.

Our findings are consistent with studies in paediatric cohorts with *KCNJ11* neonatal diabetes. Specifically, the motor features noted on neurological examination, together with impairments of attention, working memory, visuospatial ability and executive function are consistent with the previously reported high prevalence of developmental coordination disorder, inattention, executive dysfunction and poor visuomotor performance in children with *KCNJ11* mutations (12–14; 17; 18; 23; 40). ASD features in 4 individuals with

KCNJ11 mutations is consistent with previous research reporting high rates of neurodevelopmental disorders in affected children (16; 18; 41). Dyspraxia, visuomotor impairment, autism and impaired executive function may be related to the high levels of expression of dysfunctional K_{ATP} channels in the cerebellum in *KCNJ11* PNDM (7; 10).

Importantly, the abnormal findings we report in the *KCNJ11* group were mutation-specific; the 2 individuals with the R201H mutation had no overt features and only some subtle abnormalities on neuropsychological testing (Table S2). As a result, both were able to live independently and support themselves financially. Those with more severe features required high levels of support from family members and professionals in healthcare, education and social care. This is consistent with previous studies showing the severity of the CNS phenotype is related to the specific mutation; for example, the V59M mutation results in more severe features, greater impairment in daily living skills (13) and greater impact on families (16). Interestingly, however, there was a relatively good level of social integration from all patients with *KCNJ11* mutations even when the neurobehavioral features were severe.

Some of our findings contrast with previous research. To our knowledge choreiform movements have not been previously associated with *KCNJ11* PNDM but were observed in one individual with the V59M mutation in our study. We did not identify abnormal tone in our cohort, which contrasts with the hypotonia previously reported, particularly in the context of DEND/iDEND syndrome (42). This may be explained by 7/8 individuals in our study being sulfonylurea-treated; improvement in tone to near-normal following transfer from insulin to sulfonylureas has been observed in a recent study of children with *KCNJ11* PNDM (23). Similarly, improvement of visuospatial abilities and attention following transfer to sulfonylureas was noted in the paediatric study (23), which could account for the attention deficits and visuospatial impairment being less marked in our cohort of sulfonylurea-treated adults than might have been expected given previous descriptions (17; 23). Our neuroimaging findings contrast with this paediatric study in which there were non-specific findings in 12/17 who underwent brain MRI, largely comprising white matter abnormalities (23). However, these scans were performed at baseline prior to transfer to sulfonylureas (23). It is not known whether the abnormalities would have improved after a period of sulfonylurea treatment, as has been shown in SPECT studies (24; 27).

Sulfonylurea treatment may influence the CNS phenotype in *KCNJ11* PNDM. Two studies have suggested that an earlier age of initiation of sulfonylureas can lead to better CNS outcomes (17; 23). We were unable to assess this in our study because median age at transfer to sulfonylureas was 18 years (range 11-34). However, the persistence of CNS features in some patients even after early initiation of treatment (16; 23) suggests other factors are involved. Specifically, active transport of glyburide out of the brain across the blood-brain barrier, as has been demonstrated in a rodent model (28), may result in suboptimal concentrations in the CSF, thereby limiting therapeutic efficacy in the human CNS. Anecdotal clinical experience suggests that this can be partially addressed by increasing the dose of glyburide to ~1mg/kg/day; however there have been no cases of complete resolution of CNS features in a patient with iDEND. Another possible reason for the partial response is that pathways that can fully restore K_{ATP} channel function in other tissues are not available

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in the CNS to interact with brain K_{ATP} channels. For example, restoration of pancreatic K_{ATP} channel function resulting in excellent glycaemic control with sulfonylurea treatment is dependent on the activity of incretin hormones (3). Furthermore, there is a theoretical impact of insulin deficiency *in utero* and / or C-peptide deficiency prior to sulfonylurea transfer on the brain as an indirect consequence of *KCNJ11* mutations, but more studies are needed to explore this in humans. Indeed, given the complexities of human neurodevelopmental processes, it is likely that several factors contribute in some way to the response of CNS features to sulfonylureas in *KCNJ11* PNDM.

Strengths, Limitations and future work

This study has important strengths. It is the first to assess in detail the CNS manifestations of *KCNJ11* mutations in adults and to control for the non-specific effects of PNDM by comparing the features in individuals with *INS* mutations. Limitations of the study, which relate to the rarity of the disease, are the small number of individuals in each group, the broad range of mutations studied, and the variable timing of initiation and duration of treatment with sulfonylureas in the *KCNJ11* group. Studies in larger cohorts with single specific mutations would be valuable. Furthermore, exploration of the impact of treatment-specific factors, such as age of initiation, dose and CNS handling of sulfonylureas in humans, on CNS features in *KCNJ11* PNDM is warranted.

Conclusion

The CNS phenotype in adults with *KCNJ11* mutations comprises learning difficulty, autistic features, subtle motor dysfunction, moderately reduced IQ, and impaired attention, perceptual reasoning and working memory. The severity of these features varies with the causative mutation. They persist despite long term sulfonylurea therapy, at least when this is started after the first decade of life, and represent the major burden from *KCNJ11* mutations once glycemia is well controlled on sulfonylureas. These CNS features are not present in individuals with *INS* mutations, which indicates that they do not occur as a result of the lifelong metabolic disturbance imposed by PNDM, but as a consequence of impaired K_{ATP} channel function in the brain. Clinicians in adult and paediatric medicine should be aware of the potential impact of CNS features in patients with *KCNJ11* mutations and should consider multidisciplinary management to ensure appropriate support is provided.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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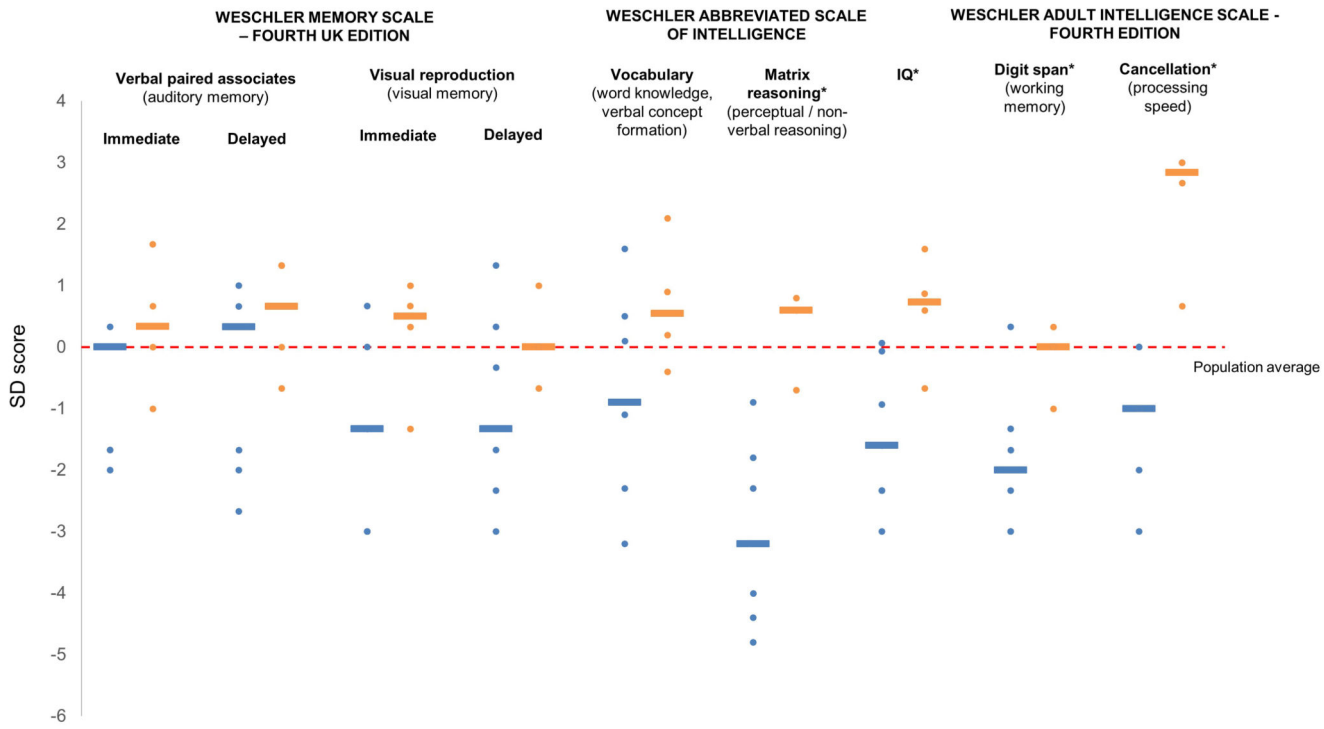

Figure 1.

Neuropsychological testing in *KCNJ11* patients (blue, n=7) and *INS* patients (orange, n=4). WMS: Verbal paired associates I/II (immediate/delayed) – auditory memory, Visual reproduction I/II (immediate/delayed) – visual memory (both components of working memory) WASI: Vocabulary - word knowledge and verbal concept formation, matrix reasoning – non-verbal/perceptual reasoning. Digit span – working memory, cancellation – processing speed. *denotes $p<0.05$ for difference between *KCNJ11* and *INS* groups.

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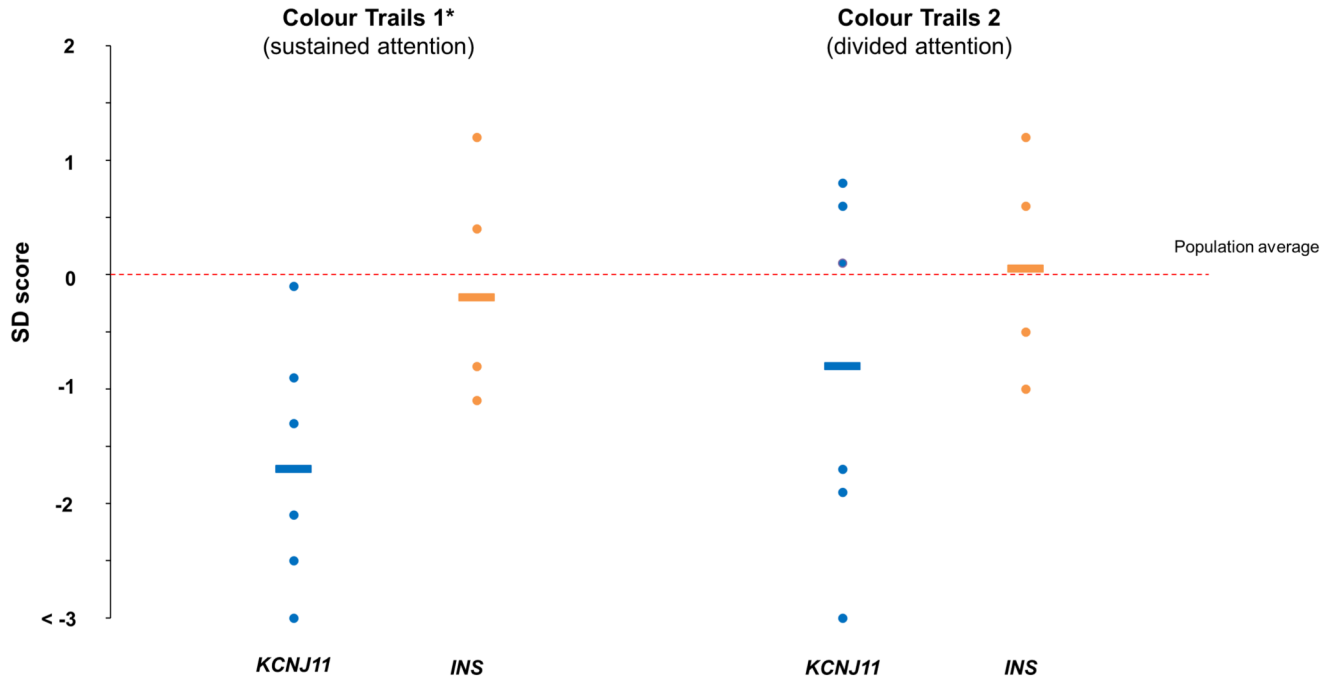

Figure 2.

Colour Trails Test 1&2 scores represented as Z-scores in the *KCNJ11* group (blue, n=6) and *INS* group (orange, n=4). Lines show group medians for each subtest; dots represent individuals. *denotes p<0.05 for difference between *KCNJ11* and *INS* groups.

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Table 1

Baseline characteristics in individual participants *KCNJ11* cases and *INS* controls and group characteristics summary.

Case	Mutation	Inheritance	Sex	Age	Age at diabetes diagnosis (weeks)	Age at genetic diagnosis (years)	Age at transfer to SU (years)	Treatment (total daily dose)	HbA1c DCCT (%)	HbA1c IFCC (mmol/mol)
KCNJ11 1	G53S	Autosomal dominant	M	32	2	23	23	Glyburide 30mg, metformin 1g	9.3	78
KCNJ11 2	R201H	Presumed *de novo*	F	22	4	15	15 (attempted)	Insulin (restarted after trial of glyburide)	8.1	65
KCNJ11 3	R201H	*De novo*	M	36	10	29	29	Gliclazide (120mg)	8.1	65
KCNJ11 4	R201C	Presumed *de novo*	F	36	5	27	34	Glyburide (40mg)	7.0	53
KCNJ11 5	R201C	*De novo*	M	19	6	13	13	Glyburide 27.5mg	5.4	36
KCNJ11 6	V252G	*De novo*	M	28	8	21	21	Glyburide (85mg)	10.8	95
KCNJ11 7	V59M	*De novo*	F	25	15	17	17	Glyburide (7.5mg)	8.1	65
KCNJ11 8	V59M	*De novo*	M	17	5	10	11	Glyburide (55mg)	5.9	41
INS 1	C43F	Autosomal dominant	F	35	78	31	N/A	Insulin	NK	NK
INS 2	F48C	Presumed *de novo*	F	50	5	42	N/A	Insulin	NK	NK
INS 3	G75C	*De novo*	M	28	8	26	N/A	Insulin	7.9	63
INS 4	H29D	*De novo*	F	20	26	12	N/A	Insulin (pump)	8.2	66
KCNJ11 group	N/A	*De novo = 7 (87.5%) Autosomal dominant = 1 (12.5%)*	M = 5 (63%) F = 3 (37%)	26.5 (17-36)	5.5 (2-15)	19 (10-29)	21 (11-34)	Insulin treated = 1/8	8.1 (5.4-10.8)	65 (36-95)
INS group	N/A	*De novo = 3 (75%) Autosomal dominant = 1 (25%)*	M = 1 (25%) F = 3 (75%)	31.5 (20-50)	17 (5-78)	28.5 (12-42)	N/A	Insulin treated = 4/4	8.1 (7.9-8.2)	65 (63-66)
P value	N/A	1.0	0.55	0.44	0.15	0.23	N/A	0.01	0.79	0.79

Summary numerical data are presented as median (range) and categorical variables are presented as n (%). Mutations were presumed to have arisen *de novo* if there was no parental history of diabetes but the mutation status of the parents had not been confirmed with a genetic test. HbA1c values are the results available closest to the time of the neurobehavioral assessment. N/A = not applicable, NK = not known.

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Table 2

History and examination findings for individual *KCNJ11* cases and *INS* controls.

Case (mutation)	HISTORY							EXAMINATION / INVESTIGATIONS	
	Developmental milestones / interventions	**Seizures (cause, if known)**	**Educational attainment**	**Learning difficulties / support**	**Employment status (job)**	**Employment status (job) of parents / siblings**	**Psychiatric history**	**Neurological examination**	**Brain MRI**
KCNJ11 1 (G53S)	D (speech and motor)	No	MS then SS (age 11)	LS (repeated year 2)	E (supermarket)	F – E (council), S – E (chemicals factory)	Repetitive hand washing and rigid routines.	Impaired motor sequencing, fine finger movements, praxis. Subtle nystagmus, dysdiadokokinesis.	ND
KCNJ11 2 (R201H)	D (speech)	No	MS then U (nursing and childcare)	LS (English until age 15, Maths for 1 year)	US	F – E (accountant) M – E (nurse)	Nil	Intermittent mild head titubation. Brisk reflexes, questionable increase in tone in left arm.	N
KCNJ11 3 (R201H)	N	Yes – hypoglycaemia on insulin	MS then C (18 months, NVQs levels 1 &2)	LS (English and Maths).	E (baker)	NK	Nil	Normal	Bilateral high T1 signal in pons – artefact
KCNJ11 4 (R201C)	N	Yes	MS then C (computing module)	LS (throughout school)	E (pubs, shops, hotel)	B – E (operations manager), S – E (sports complex manager)	Depression – Sertraline 50mg. Occasional auditory hallucinations.	Nystagmus (2-3 beats on horizontal gaze), subtle intention tremor.	N
KCNJ11 5 (R201C)	D (gross motor, speech).Speech therapy.	Yes – hypoglycaemia on insulin	MS then C (for people with ID)	LS (from age 10).	CS (college for people with ID).	F – E (company manager), M - UE (housewife), B – E (aviation engineer), B – US (political science)	Anxiety (social skills training by psychologist)	Impaired motor sequencing.	ND
KCNJ11 6 (V252G)	D (speech, fine motor). Speech therapy.	No	SS then school for autistic children	Unable to read/ write. Supported accommodation.	UE	B – E (carpenter)	Autism	Impaired motor sequencing, praxis, heel-toe walking. Hand-flapping.	ND
KCNJ11 7 (V59M)	Speech therapy.	Yes – hypoglycaemia on insulin	MS then C (1st year - childcare)	LS (throughout school)	E (SS teaching assistant)	M – E (SS teaching assistant), F – E (lecturer), B – E (trainee lawyer)	Anxiety	Impaired motor sequencing, dysdiadokokinesis, choreiform movements.	N (movement artefact)
KCNJ11 8 (V59M)	D (global).	Yes – hypoglycaemia on insulin	SS	Unable to read/ write.	UE	S – E (museum curator)	Autism	Ritualistic, clumsy, echolalia. Generally	ND

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Case (mutation)	HISTORY							EXAMINATION / INVESTIGATIONS	
	Developmental milestones / interventions	**Seizures (cause, if known)**	**Educational attainment**	**Learning difficulties / support**	**Employment status (job)**	**Employment status (job) of parents / siblings**	**Psychiatric history**	**Neurological examination**	**Brain MRI**
								uncooperative with examination.	
INS 1 (C43F)	N	Yes	U (pharmacy degree)	No	E (hospital pharmacist)	NK	Nil	Normal	ND
INS 2 (F48C)	N	Yes – hypoglycaemia	U (law degree)	No support.	UE (ill health). Clerical / carer jobs in past	F – E (taxi business manager, security guard)	Depression (medication and CBT in the past), OCD	Depressed leg reflexes (in-keeping with known diabetic neuropathy).	Left temporal lobe abnormality – CSF space or artefact
INS 3 (G75C)	N	No	MS	No support.	E (dept. of work and pensions)	F – E (carpenter, transport manager), B – E (marketing agency)	Nil	N	N
INS 4 (H29D)	N	Yes – DKA	MS	LS (Maths & English 4 years).	E (bank call centre)	F – E (carpenter)	Anxiety, panic attacks (Escitalopram in the past)	N	Prominent left cerebellar sulcus, periventricular white matter lesions

NK = not known, ND = not done, D=delayed, N=normal, MS = Mainstream school, SS = Special school, U = University, C = College, LS = learning support, E = employed, UE = unemployed, ID = intellectual disability, US = university student, CS = college student, OCD = obsessive compulsive disorder, DKA = diabetic ketoacidosis, F = father, M = mother, B = brother, S = sister