HNF1B whole-gene deletions are associated with autistic traits

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Introduction

- Heterozygous mutations and deletions of the *HNF1B* gene result in a multi-system disorder and are the commonest monogenic cause of developmental kidney disease.[1]
- Increasing interest has focused on whether *HNF1B* gene anomalies are associated with neuropsychological conditions.
- A 1.4 Mb deletion at chromosome 17q12, which includes *HNF1B*, confers an increased risk of autism and cognitive impairment.[2]
- Recent work suggests that when children are diagnosed with a 17q12 deletion secondary to kidney abnormalities, the neurodevelopmental phenotype is less severe than that previously reported.[3]
- The deleted stretch of DNA contains 15 genes and it is not clear what genetic mechanism gives rise to this neuropsychological phenotype.

Aims

- To assess neuropsychological disorders in children and adults with either an *HNF1B* mutation or whole-gene deletion under follow-up with nephrology or diabetes services.

Methods

- 35 patients (age range 4-65 years) with known *HNF1B* coding region/splice site mutations (n=16) or whole-gene deletions (n=19) from 4 UK centres were compared.
- Autistic traits were assessed using the Autism-Spectrum Quotient (AQ).
- Cognitive ability was assessed using the Kaufman Brief Intelligence Test, Second Edition.
- Brief behavioural screening was carried out in 4-16 year olds only using the Strengths and Difficulties Questionnaire.
- Facial photographs of the patients were taken and analysed by a clinical geneticist.
- Results were analysed using the unpaired t-test and Fisher's exact test.

Results

GENERAL CHARACTERISTICS (TABLE 1)

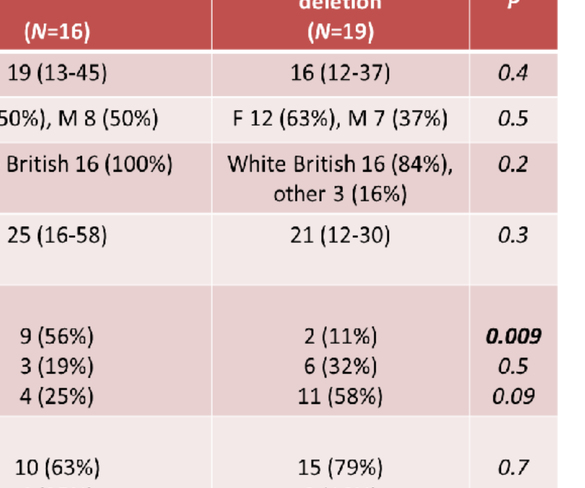
	HNF1B mutation (*N*=16)	*HNF1B* whole-gene deletion (*N*=19)	*P*
Median age, years (IQR)	19 (13-45)	16 (12-37)	*0.4*
Sex, *N* (%)	F 8 (50%), M 8 (50%)	F 12 (63%), M 7 (37%)	*0.5*
Ethnicity, *N* (%)	White British 16 (100%)	White British 16 (84%), other 3 (16%)	*0.2*
Median Indices of Deprivation 2007 score (IQR)	25 (16-58)	21 (12-30)	*0.3*
Inheritance, *N* (%)			
From affected parent	9 (56%)	2 (11%)	***0.009***
De novo	3 (19%)	6 (32%)	*0.5*
Unknown	4 (25%)	11 (58%)	*0.09*
Renal abnormality, *N* (%)			
Cysts	10 (63%)	15 (79%)	*0.7*
Other*	4 (25%)	3 (16%)	
Median age at diagnosis of renal disease, years (IQR)	0 (0-22)	0 (0-26)	*0.8*
Diabetes, *N* (%)	6 (38%)	7 (37%)	*1*
Median age at diagnosis of diabetes (IQR)	20 (18-43)	31 (19-33)	*0.9*

Abbreviations: F, female; IQR, interquartile range; M, male.
*Other renal structural abnormalities included cystic dysplasia, single kidney, collecting system abnormalities and bilateral hydronephrosis; in 3 cases the imaging results were not known.

- Both groups were similar in terms of age, gender, ethnicity, Indices of Deprivation 2007 score, renal disease and diabetes.
- Inheritance from an affected parent was more common in patients with an *HNF1B* gene mutation (56% *versus* 11% in deletion group, *P*=0.009).

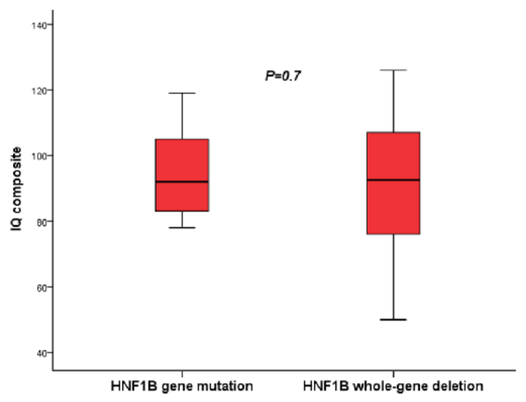
AUTISTIC TRAITS (FIGURE 1)

- Patients with an *HNF1B* whole-gene deletion had a higher median AQ (45.9% *versus* 28.7% in the mutation group, *P*=0.006), indicating a greater number of autistic traits.



COGNITIVE ABILITY (FIGURE 2)

- The median IQ composite was similar in both groups (92 in mutation group *versus* 92.5 in deletion group, *P*=0.7).



BEHAVIOURAL SCREENING (TABLE 2)

- The likelihood of a probable emotional, behavioural or hyperactivity/concentration disorder was similar in both groups but the numbers were very small.

	HNF1B mutation (*N*=7)	*HNF1B* whole-gene deletion (*N*=10)	*P*
Mean parental total difficulties score (SD)[a]	7.3 (0.6)	15.7 (9.8)	*0.2*
Mean child total difficulties score (SD)[b]	14.7 (7.2)	15.7 (13.2)	*0.9*
Mean parental impact score (SD)[c]	0	4.7 (3.1)	***0.03***
Mean child impact score (SD)[c]	0.7 (1.2)	2.7 (3.8)	*0.4*
Prediction to any disorder, *N*			
Probable	1	5	*1*
Possible or unlikely	2	4	

Abbreviations: SD, standard deviation.
[a] 0-13 is a close to average score; [b] 0-14 is a close to average score; [c] 0 is a close to average score.

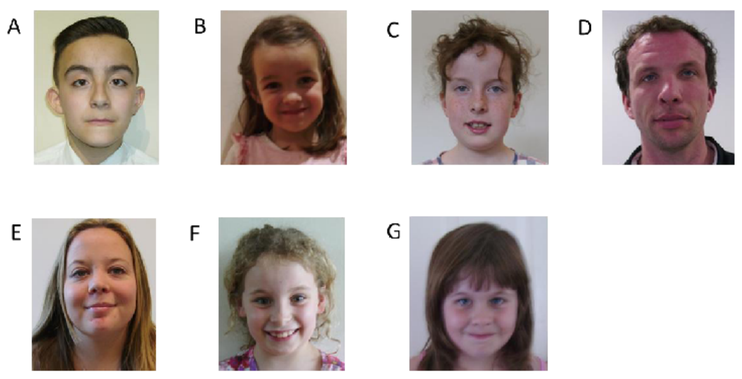
Table 2. Strengths and Difficulties Questionnaire results

CLINICAL DIAGNOSIS

- 6/19 (31.6%) patients with a whole-gene deletion had a clinical diagnosis of either an autism spectrum disorder (ASD) and/or attention deficit hyperactivity disorder (ADHD) (*versus* 0/16 patients with a mutation, *P*=0.02).
- The prevalence rate of autism in the UK is 1.1%[4]; the estimated pooled prevalence of ADHD was 7.2% in a recent meta-analysis[5].

FACIAL PHENOTYPE (FIGURE 3)

- Three mild facial dysmorphic features previously described in patients with a 17q12 deletion (prominent forehead, arched and high eyebrows, long face)[2,3] were seen in the whole-gene deletion group but not the mutation group.



- **Figure 2. Photographs of 7 patients with an *HNF1B* whole-gene deletion. A prominent forehead (cases A-F), arched and high eyebrows (cases A and E) and a long face (cases A, C and D) were seen. Case A also had down-slanting palpebral fissures.**

Conclusions

- Patients with whole-gene deletion of *HNF1B* displayed a greater number of autistic traits than those with *HNF1B* mutations.
- IQ composite scores were similar between the 2 groups.
- The frequency of ASD and ADHD in the whole-gene deletion group is much greater than the population prevalence; this suggests that the neuropsychological phenotype in patients with a 17q12 deletion diagnosed secondary to kidney problems or diabetes is more severe than previously reported.[3]
- These results indicate it is not haploinsufficiency of the *HNF1B* gene that is responsible but another genetic mechanism yet to be determined.
- Nephrologists should be aware of this association to ensure referral to psychiatric services can be made where applicable.

References

- 1. Clissold, R. L. et al. Nat Rev Nephrol 11, 102–112 (2015)
- 2. Moreno-De-Luca, D. et al. Am J Hum Genet 87, 618–630 (2010)
- 3. Laffargue, F. et al. Arch Dis Child 0, 1-6 (2014)
- 4. www.autism.org.uk
- 5. Thomas, R. et al. Pediatrics 135, e994-e1001 (2015)

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