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Short Report

New insights into Brunner syndrome and potential for targeted therapy

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We report two families with Brunner syndrome living in one state of Australia. The first family had a predicted protein-truncating variant of monoamine oxidase A (*MAOA*) (p.S251KfsX2). Affected males had mild intellectual disability (ID), obsessive behaviour, limited friendships and were introverted and placid during clinical interview. The family disclosed episodic explosive aggression after a diagnosis was made. The second family had a missense variant in *MAOA* (p.R45W). Affected males had borderline-mild ID, attention deficit disorder and limited friendships. One had a history of explosive aggression in childhood and episodic symptoms of flushing, headaches and diarrhoea. Their carrier mother had normal intelligence but similar episodic symptoms. Characteristic biochemical abnormalities included high serum serotonin and urinary metanephrines and low urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA). Symptomatic individuals in the second family had particularly high serotonin levels, and treatment with a serotonin reuptake inhibitor and dietary modification resulted in reversal of biochemical abnormalities, reduction of 'serotonergic' symptoms and behavioural improvement. Brunner syndrome should be considered as a cause of mild ID with paroxysmal behavioural symptoms. It can be screened for with serum/urine metanephrine and serotonin measurement. Cautious treatment with a serotonin reuptake inhibitor, dietary modifications and avoidance of medications contraindicated in patients on monoamine oxidase inhibitors can improve symptoms.

Conflict of interest

All authors declare no conflict of interest.

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Key words: autism spectrum disorder – Brunner syndrome – diagnosis – intellectual disability – MAO-A deficiency – serotonin – treatment

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Brunner syndrome (OMIM 300615) was first described in 1993 in a large Dutch kindred. Linkage to Xp11-21 was obtained, and biochemical evidence of monoamine oxidase A (MAOA) deficiency and a subsequent protein-truncating variant in the *MAOA* gene was identified (1, 2). The affected males had non-syndromic borderline-mild intellectual disability (ID) with stress-induced aggressive outbursts. Aberrant sexual behaviour and episodic night terrors were characteristic. Subsequently, there has been debate regarding possible influences of polymorphisms in the *MAOA* gene and behavioural dysinhibition, especially in the context of childhood stress exposure (3, 4). Brunner syndrome because of pathogenic variants in the *MAOA* gene has been infrequently observed despite active screening of X-chromosome-linked intellectual disability (XLID) cohorts (5). We are aware of two further reports: one family, genetically characterised herein, and previously only identified biochemically (6) and another recent case report (7) of males with variable ID/autism spectrum disorder, aggressive behaviour, a missense variant in *MAOA* and abnormal urinary monoamines.

There are two genes coding for two specific isoforms of monoamine oxidase (MAO), *MAOA* and *MAOB*, located at Xp11.2. The MAO enzymes have key roles in oxidative deamination of the neurotransmitters serotonin, dopamine, adrenaline and noradrenaline, as well as metabolising minor amines including tyramine. MAOA is more biologically active and loss of function of MAOB alone because of a partial gene deletion has not been associated with biochemical or clinical sequelae (8).

Materials and methods

Clinical description of the families

Family H

The pedigree (Fig. 1) consisted of two non-dysmorphic well-grown brothers III:1, 59 years, and III:4, 52 years, with mild ID and essential tremor (clinical details Table 1). They had an affected maternal uncle (II:3) who died at 60 years of age following a motor vehicle accident (unavailable for genetic testing). Notably, behaviour problems were not reported on initial assessment with both males appearing very passive during clinical interview. Direct questioning later revealed III:1's history of impulsivity, school expulsions and violent episodes involving property damage and aggression towards family members. III:4 had a history of explosive temper, affecting his ability to maintain employment, as well as limited interests and obsessive behaviour with significant hoarding. III:4 would occasionally become infatuated with female acquaintances. Both males had difficulties with sleep onset but no history of night terrors. Neither affected male had stereotypical hand movements although III:4, repetitively, combs his hair and both have infrequent involuntary body twitches and essential tremor. No anti-depressant or psychotropic medication had been prescribed. No specific serotonergic symptoms or worsening of behaviour with high tyramine foods or medication were noted.

Family R

This family was previously reported by Cheung and Earl (6). An adult female patient of normal intelligence presented with paroxysmal episodes of flushing, diarrhoea, headache and palpitations. She was initially suspected to have carcinoid syndrome, but urinary 5-hydroxyindoleacetic acid levels, abdominal and chest computerized tomography (CT) scans, and somatostatin receptor scan were normal. Further investigation identified raised serum and platelet serotonin and low levels of serotonin metabolites compatible with MAOA deficiency. We recently reviewed this family (Table 1). III:4 has two adult sons aged 33 (IV:5) and 31 (IV:6) years, both of whom have borderline-mild ID and attention-deficit hyperactivity disorder (ADHD). IV:5 had a history of impulsive behaviour and aggressive outbursts in childhood initially treated as epileptic without any noticeable benefit from medication. From adolescence, IV:5 had symptoms of episodic flushing, diarrhoea and headache. IV:6 had difficulties sustaining friendships and obsessive symptoms. IV:5 had recurrent severe nightmares from childhood into adolescence. Neither affected male had persistent abnormal sexual behaviour although neither have had a sustained relationship with a female partner. Neither affected male have stereotypical hand movements; both have an essential tremor (as does their unaffected father), and IV:5 has occasional finger and leg 'twitches'.

All affected individuals in Family R notice an exacerbation of serotonergic symptoms when they consume food and drink high in tyramine, especially beer, cheese and 'vegemite' (yeast extract). These foods were a trigger for the aggressive outbursts for IV:5. Patients III:4, IV:5 and IV:6 were cautiously commenced on 50 mg/day of sertraline, a selective serotonin reuptake inhibitor (SSRI). The dose of medication was very slowly increased under hospital admission supervision. There were initial exacerbation of serotonergic symptoms, but then III:4 and IV:5 (the more severely affected individuals) reported reduction in the frequency of headaches and flushing, severity of diarrhoea and improvement in mood. A reduction in aggressive outbursts for IV:5 was noted by his family. III:4 reported similar beneficial effects on venlafaxine (37.5 mg/day increased to 75 mg/day). Complete normalisation of biochemistry was demonstrated on treatment with sertraline (6); however, even on treatment, affected individuals report re-emergence of milder serotonergic symptoms with dietary indiscretions.

III:5 was recently briefly trialled off sertraline 10 years after treatment was commenced, on request of his family. Repeat bioamine profiling (on and off SSRI medication) demonstrated a normalisation of serum serotonin and normetanephrine/metanephrine on medication and re-elevation off medication (Fig. 2 and Table S1, Supporting Information). Off medication, he had frequent episodes where he was flushed, diaphoretic, disorientated, tachycardic and mildly hypertensive, and often unable to work.

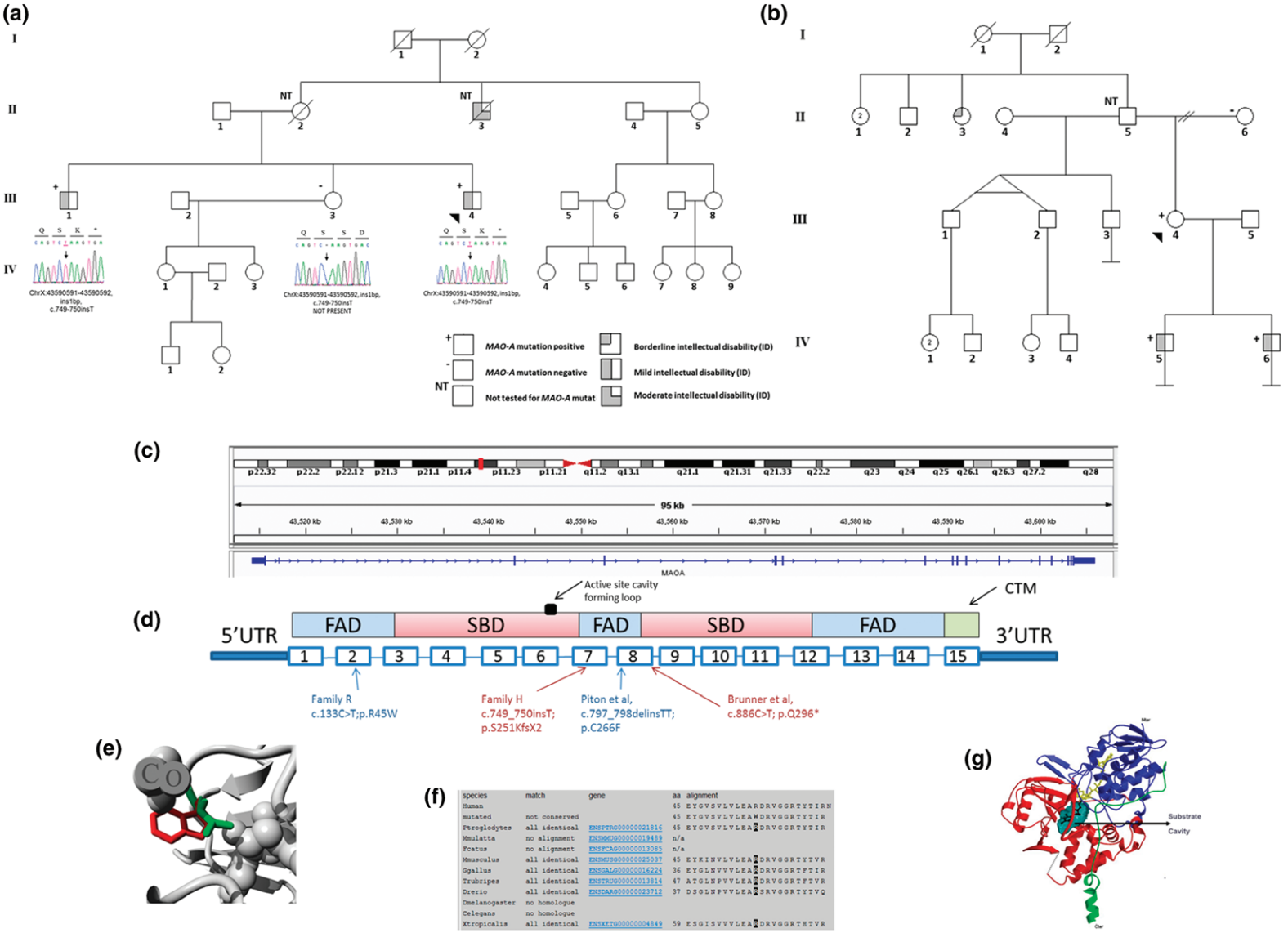


Fig. 1. Legend on next page.

X-exome sequencing

Family H

The proband from this family, III:4, was investigated by X-chromosome exome capture as described in Hu et al. (9).

Sanger sequencing

Family H

DNA extracted from whole-blood (QIAamp DNA blood maxi kit; Qiagen, Limburg, The Netherlands) was part of a large X-chromosome exome sequencing study (9). Only one affected individual was sequenced (Illumina GAIIx; Max Planck Institute for Molecular Genetics, Berlin, Germany). Confirmation of variants by Sanger sequencing was carried out using standard methods.

Family R

DNA was extracted from lymphocytes, and DNA Sanger sequencing of the *MAOA* gene (NM_000240.2) was performed using standard methodology (Laboratorium Genoomdiagnostiek, UMS St Radboud, Nijmegen, The Netherlands).

Bioamine assays

Plasma noradrenaline and adrenaline levels, serum serotonin levels, and urine levels of catecholamines, metanephrine, normetanephrine and 5HIAA levels were quantitated by high-performance liquid chromatography (HPLC) with electrochemical detection. Plasma metanephrine and normetanephrine levels were quantitated by liquid chromatography–mass spectrometry (LCMS).

Results

Family H

A single base pair insertion in exon 5 of the *MAOA* gene was identified. This DNA variant is predicted to result in a truncated MAOA protein, c.749-750insT; p.S251KfsX2 (using NM_000240) (Fig. 1d).The variant was present in both males, and their mother was assumed to be an obligate carrier.

The deleterious effect of the variant was confirmed by profiling the bioamine levels in blood and urine in this family (Fig. 2 and Table S1). These biochemical results are similar to those previously reported by patients with Brunner syndrome (1, 6, 7; Fig. 2 and Table S1).

Family R

Sequencing revealed a rare novel missense variant c.133C>T (p.Arg45Trp) in *MAOA* (transcript ENSP00000340684) (Fig. 1d). This variant is not present in the ExAC dataset [Exome Aggregation Consortium, Cambridge, MA (http://exac.broadinstitute.org), accessed December 2014], affects an evolutionarily conserved residue (down to Xenopus) (Fig. 1f) and is predicted to have a functional impact based on *in silico* prediction software including PROVEAN [Protein Variation Effect Analyser (http://provean.jcvi.org/index.php)] (predicted pathogenic – score −6.7) and MUTATIONTASTER [Mutation Taster (http://mutationtaster.org/)] (disease causing). The variant introduces a larger and more hydrophilic amino acid in the oxidase [flavin adenine dinucleotide (FAD) binding] domain of the protein (Fig. 1g), predicted to impact on substrate binding and protein folding (Fig. 1e). The variant was present in both affected males, and their symptomatic mother; but not present in the maternal grandmother. The maternal grandfather was unavailable for testing. All variants have been submitted to CLINVAR [ClinVar (www.ncbi.nlm.nih.gov/clinvar/].

Bioamine levels for affected family members are summarised in Fig. 2 (detailed information in Table S1). MAOA substrates serotonin and normetanephrine were elevated, and bioamine metabolites were in the low normal range. The effect on serotonin metabolism was more marked than that on catecholamine metabolism.

Discussion

Brunner syndrome has been an uncommonly diagnosed cause of XLID with only two new cases reported in the last 20 years (6, 7). The identification of at least two cases in the Australian state of New South Wales suggests that the scarcity of cases may represent problems with ascertainment, rather than rarity of the phenotype. In both of the families that we report, the degree of developmental delay in affected males was mild and semi-open

Fig. 1. Pedigrees of the two families and characterisation of *MAOA* variants. (**a**) Pedigree for Family H showing Sanger results of *MAOA* sequencing. Primers flanking *MAOA* exon 7 were used to amplify and sequence gDNA, F – 5′-TGG CCT GTG ACT TTC TGG A-3′ and R – 5′-GCA GGC GTG AAA AAT CAT CT-3′. Arrow indicates nucleotide variant site (Hg19: ChrX: 43590591–43590592, ins1bp, p.S251KfsX2). (**b**) Pedigree for Family R. (**c**) Position of *MAOA* gene on X-chromosome (integrative genomics viewer, IGV); (**d**) location of functional domains of MAOA protein and position of variants for Family R and H and those described by Brunner *et al.* (2) and Piton *et al.* (7). FAD (blue boxes) = flavin adenine dinucleotide binding domains: residues 13–88, 220–294, and 400–462; SBD (red boxes) = substrate-binding domain: residues 89–219 and 295–399; CTM (green box) C-terminal membrane region: residues 463–506. The active site cavity-shaping loop (residues 210–216) is depicted as black box. The missense variant for Family R lies within a FAD-binding domain, as does the missense variant for the family described by Piton *et al.* (7). (**e**) Close-up of the predicted structural effect of Family R variant (R45W) – the missense variant is predicted to introduce a larger, more hydrophobic residue that will cause an ionic interaction within the protein to be lost. The protein is coloured grey, the side chains of both the wild-type and the mutant residue are shown and coloured green and red, respectively (16); (**f**) conservation of residue R at position 45 (highly conserved down to *Xenopus tropicalis*) (15) (**g**) Reprinted with permission from Edmondson, Binda and Mattevi, 2007. Ribbon diagram of human MAOA protein, colours follow descriptions in **b**. R arginine, W, tryptophan.

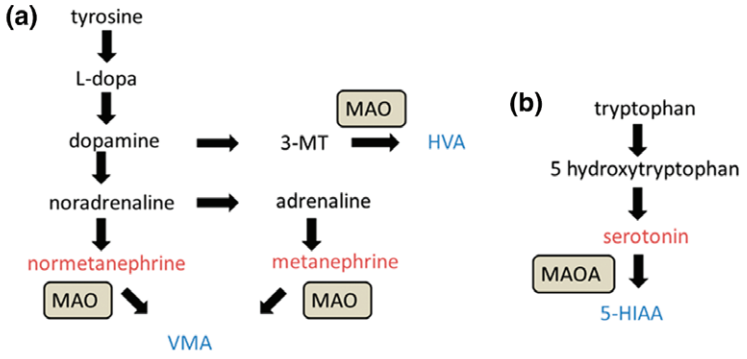
Table 1. Phenotypic information regarding affected members of Family H and Family R, and carrier mother in Family R, compared with affected individuals and carrier females in families described by Piton et al. (7) and Brunner et al. (1)

	Family H III:1 (affected male)	Family H III:4 (affected male)	Family R III:4 (carrier female)	Family R IV:5 (affected male)	Family R III:6 (affected male)	Affected males Brunner et al. (1)	Affected males Piton et al. (7)
Pregnancy/birth	Uncomplicated pregnancy, term delivery. BW 2.5 kg, suspected neonatal cerebral bleed but no persistent neurological signs.	Uncomplicated pregnancy, term delivery. BW 3.2 kg.	Uncomplicated pregnancy. Normal birth parameters.	Prematurity (34 weeks). No neonatal complications, normal birth parameters for gestational age.	Prematurity (34 weeks). No neonatal complications, normal birth parameters for gestational age.		Prematurity in all affected males.
Developmental level/schooling	Mild intellectual disability. Support class. Limited literacy.	Mild intellectual disability. Support class. Dyslexia. 'inattentive at school'.	Normal intelligence	Mild intellectual disability. ADHD. Not literate or numerate.	Borderline intellectual disability. Dyslexia. Support class. ADHD. Limited literacy and numeracy skills.	Borderline to mild intellectual disability in affected males, carrier females all normal intelligence.	Variable intellectual disability in affected males (selective cognitive deficits to severe ID). ADHD proband. Carrier mother of proband normal intelligence.
Behavioural/personality/ sleep issues	History of impulsivity, frequent school expulsions, violent episodes, damage to family home. Few friends. Disturbed sleep/wake cycle.	Explosive temper. Limited interests. Hoards books. Few friends. Described as quiet and thoughtful. Disturbed sleep/wake cycle.	NR	History of impulsivity and aggressive outbursts with high tyramine foods. Otherwise generally placid. Severe nightmares in childhood and adolescence.	Limited friends. Some obsessive traits. Generally placid.	Repeated episodes of aggressive, sometimes violent behaviour, associated with night terrors. Relatively placid, withdrawn and shy, often without friends.	Affected males: autism spectrum disorder. Auto- and hetero-aggressive behaviours.
Employment/ accommodation	Previously sheltered workshop, now unemployed. Lives at home with father.	No stable employment. Lives alone.	Lives with husband	Sheltered employment. Supported accommodation.	Open employment as horticulturalist. Lives with parents.	All but one affected male unable to sustain regular employment.	No independent employment or accommodation for affected males.
Neurological symptoms including epilepsy	'Clumsy', occasional body twitches. Essential tremor.	'Clumsy', occasional body twitches. Essential tremor. Compulsive hair combing.	Persistent left hemiplegia after haemorrhagic stroke.	Essential tremor. Rage episodes initially treated as epileptic without supportive EEG/MRI brain findings or amelioration with AED. Occasional body twitches.	Essential tremor.	Tendency to hand wringing, plucking or fiddling.	Dystonic movements of head and hands attributed to secondary effect of medication. Hand stereotypies.
Mental health symptoms	None formally diagnosed.	None formally diagnosed.	Depression	None formally diagnosed.	None formally diagnosed.	None formally diagnosed.	Maternal grandmother of proband depression and psychotic disturbance.

Table 1. Continued

	Family H III:1 (affected male)	Family H III:4 (affected male)	Family R III:4 (carrier female)	Family R IV:5 (affected male)	Family R III:6 (affected male)	Affected males Brunner et al. (1)	Affected males Piton et al. (7)
Flushing/diarrhoea/ headache symptoms	NR	NR	Yes (severe)	Yes from adolescence (severe off SSRI)	Occasional	NR	NR
Hypertension	Mild	NR	Yes	Yes (off SSRI)	No	NR	NR
Medication affecting bioamine pathways	None	None	Previously on sertraline currently on venlafaxine and pregabalin	Sertraline (SSRI) normalised serotonin	Sertraline (SSRI) normalised serotonin	NR	'Psychotropic and sedative drugs stabilised behavioural aggravation' in affected males.
Other medical issues	Hypercholesterolaemia		Hypercholesterolaemia, AI hypothyroidism.	Right cholesteatoma and unilateral hearing loss.		1 with unilateral clubfoot.	NR
Growth parameters	OFC 57 cm (75th centile, height 172 cm (50–75th centile). Overweight.	OFC 57 cm (75th centile), height 169 cm (50-75th centile). Overweight.	Normal growth parameters	OFC 60 cm (>98th centile), height 174 cm (50th centile). Overweight ++	OFC 60 cm (>98th centile), 180 cm tall (75th centile).	Normal growth parameters.	Adult affected males, OFC-2SD, overweight.
Dysmorphism?	Non-dysmorphic	Non-dysmorphic	Non-dysmorphic	Non-dysmorphic	Non-dysmorphic	Non-dysmorphic	Non-dysmorphic
Other normal genetic testing	Karyotype, chromosomal microarray, X tiling path microarray, fragile X and *FRAXE* PCR, 6 ID gene mutation screen.	Chromosomal microarray, fragile X PCR		Chromosomal microarray, fragile X PCR, urine organic acids, amino, GAG screen and creatine metabolites.	Chromosomal microarray, fragile X PCR, urine organic acids, amino, GAG screen and creatine metabolites.	Karyotype	
MAOA mutation	c.749_750insT; p.S251KfsX2 (hemizygous)	c.749_750insT; p.S251KfsX2 (hemizygous)	c.133C>T; p.Arg45Trp (heterozygous)	c.133C>T; p.R45W (hemizygous)	c.133C>T; p.R45W (hemizygous)	c.886C>T; p.Q296*	c.797_798delinsTT; p.C266F
Predicted effect of MAOA mutation	Truncating mutation	Truncating mutation	Missense mutation affecting oxidase domain	Missense mutation affecting oxidase domain	Missense mutation affecting oxidase domain	Truncating mutation	Missense mutation (affecting FAD-binding protein domain)
Summary of bioamine aberrations	High serotonin, metanephrine and normetanephrine. Low HVA, VMA, 5-HIAA	High serotonin, metanephrine and normetanephrine., low HVA, VMA, 5-HIAA	High serotonin and normetanephrine.	High serotonin and normetanephrine.	High serotonin and normetanephrine.	High serotonin and normetanephrine, low HVA, VMA, 5-HIAA	High metanephrine and normetanephrine, serotonin not tested, low VMA, 5-HIAA.

ADHD, attention-deficit hyperactivity disorder; AED, anti epileptic drugs; AI, autoimmune; BW, birth weight; EEG, electroencephalography; FAD, flavin adenine dinucleotide; GAG, glycosaminoglycans; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; ID, intellectual disability; MAOA, monoamine oxidase A; MRI, magnetic resonance imaging; NR, not recorded; NT, not tested; OFC, occipitofrontal circumference; PCR, polymerase chain reaction; SSRI, selective serotonin reuptake inhibit; VMA, vanillylmandelic acid; XLID X-chromosome-linked intellectual disability.



(c)

	Family H	Family R (off medication)	Family R (on medication)	Brunner family	Piton family
dopamine	→	→	→	NT	NT
HVA	↓	→	NT	↓	→
serotonin	↑	↑	→	↑	↑
5-HIAA	↓	→	→	→	↓
normetanephrine	↑	↑	→	↑	↑
metanephrine	↑	↑	→	↑	↑
VMA	↓	↓	NT	↓	↓/→

Fig. 2. Changes in bioamine metabolism in patients with monoamine oxidase A (MAOA) deficiency. (**a**) Serotonin metabolism pathway with changes in metabolites detected in patients affected by MAOA deficiency. MAOA substrate serotonin (red) elevated and breakdown product 5-hydroxyindoleacetic acid (5-HIAA) (blue) decreased or unchanged. (**b**) Catecholamine metabolism pathway with changes in metabolites detected in patients affected by MAOA deficiency. MAOA substrates normetanephrine and metanephrine (red) elevated and breakdown products vanillylmandelic acid (VMA) and homovanillic acid (HVA) (blue) decreased or unchanged. (**c**) Comparison of bioamine metabolite results for affected patients in Family H, R, Brunner et al. (1) and Piton et al. (7) families. Elevations in MAOA substrates normetanephrine, metanephrine and serotonin levels are the most consistent biochemical signature for MAOA deficiency. These metabolite levels were completely normalised in affected individuals from Family R treated with a selective serotonin reuptake inhibitor (SSRI) (column 4). Absolute values are listed in Table S1. NT, not tested.

employment, and independent living was possible. It is conceivable that the cohorts of patients that have previously been screened for Brunner syndrome had more significant cognitive disability. There has also been debate and potential misinterpretation of the behavioural characteristics of affected males (10, 11): episodic impulsive behaviour leading at times to physical aggression seems to be the most important behavioural clue. Affected males also had autistic features, including lack of friendships, difficulties interpreting female relationships, narrow interests and obsessional collecting. Similar characteristics were reported in the family described by Piton (7). Parasomnias, including night terrors, and subtle neurological symptoms of tremor, stereotypical hand movements or occasional body twitches also appear to be characteristic. Abnormal bioamines are an effective way to follow up the significance of any detected variants in *MAOA* (e.g. from genomic screening).

Specific questioning regarding 'serotonergic syndrome' symptoms (episodic flushing, headaches and diarrhoea) and the exacerbation of physical and behavioural symptoms with high tyramine-containing foods and drinks, such as cheese and yeast extract, may also be diagnostically helpful. These symptoms are not mentioned in the case reports of Brunner and Piton, but may not have been specifically elicited. Serotonergic symptoms may not be universal for Brunner syndrome: there may be genotype–phenotype correlation. They were not present in affected members of Family H, who had a loss of function variant, but were prominent in Family R who had a missense variant. The affected members of Family R had particularly high serotonin levels off medication. It is possible that the conformational change of the oxidase-binding site in affected members of Family R may selectively affect serotonin metabolism more than other bioamines (Fig. 2). The *MAOA* missense variant Y444F has such a specific effect (12). Additional functional work and evaluation of further clinical cases is required to investigate this further.

We suggest that behavioural issues in individuals affected by Brunner syndrome are related to elevated serotonin, although the mechanism is incompletely understood at the synaptic level. Elevated platelet serotonin has been associated with autism spectrum disorder (13) and a low efficiency promoter region polymorphism within the *MAOA* gene associated with autism severity and aggression (14). An MAOA-deficient mouse model suggests serotonin elevation may result in an increase in the frequency and intensity of physical aggression between male mice (15).

The amelioration of physical and behavioural symptoms with SSRI/SNRI (seratonin-norepinephrine reuptake inhibitor) medication in Family R is difficult to explain comprehensively. This appears paradoxical, as the anti-depressant/anti-anxiolytic effect of this medication is postulated to be because of an increase of monoamines at brain synapses, and these medications are contraindicated in patients taking a monoamine oxidase inhibitor due to the risk of precipitating serotonergic syndrome. However, there is supportive animal model data that administration of the SSRI fluoxetine reduces aggressive behaviour and perseverative responses in *MAOA* knockout mice and improves social deficits and perseverative responses in mice with a hypomorphic *MAOA* variant (16). The authors were surprised by this treatment effect as they had anticipated that the SSRI would worsen symptoms.

Earl and Cheung (6), who originally recommended a therapeutic trial of SSRI in Family R, postulated that symptoms related to serotonergic excess would be reduced over time because of reduction of peripheral serotonin. Blood serotonin levels fall in individuals treated with SSRI's due to inhibition of platelet serotonin transporters, platelets being the major storage site of serotonin in the blood (17). The exact effect of SSRI/SNRI medication acutely and chronically in different brain regions even in individuals with normal MAOA function is far from understood (18), and it is difficult to say whether improvements in mood and behaviour in treated members of Family R were purely because of relief of physical symptoms or an additional central effect.

Cautious treatment with an SSRI may be useful in other families with Brunner syndrome, particularly in individuals with high serotonin levels and debilitating 'serotonergic symptoms'. Such treatment trials carry the risk of precipitating life-threatening serotonergic syndrome as patients with Brunner syndrome likely have increased stores of serotonin because of loss of MAOA function. We would recommend that an SSRI/SNRI be started at the lowest possible dose with very slow escalation and close cardiovascular and neurological monitoring over at least a 2-week hospital admission.

The potential of tyramine-containing foods and certain medication (those contraindicated in patients on a monoamine oxidase inhibitor) to precipitate potentially life-threatening serotonergic symptoms points to the additional medical importance of diagnosing Brunner syndrome. We would advise individuals diagnosed with Brunner syndrome to be referred to a dietician, avoid medication contraindicated in patients on monoamine oxidase inhibitors unless under strict medical supervision and be issued with 'Medic-Alert' bracelets.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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